An Economic Strategy to Develop Non-Timber Forest Products and Services in British Columbia

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Final Report

(This strategy can be downloaded from
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PART II. THE ECONOMIC STRATEGY

Executive Summary

This report describes some of the most economically-valuable non-timber forest products and services emerging from BC wildlands and analyses their associated industries, production technologies and markets. It then presents an economic strategy for rapid development of these industries.

The products and services highlighted are:

- wild food mushrooms
- nutraceutical and medicinal mushrooms (*mycomedicinals*) and fungi
- nutraceuticals and pharmaceuticals from plants, bark, lichens, insects, soil organisms, and wood waste
- biocides (non-toxic insecticides) from the same sources
- anti-phytovirals (medicines *for* plants)
- floral greenery
- ecotourism

The term *nutraceutical* broadly means a substance with both nutritional and therapeutic benefits, something one consumes when healthy to remain so or get healthier. Nutraceutical food products and herbal supplements had estimated global sales of between US $10-$12 billion in 1998, and a variety of popular nutraceuticals are found on BC wildlands. Saskatchewan, Alberta and several US states are actively supporting their nutraceutical companies.

Emerging products and industries typically have high risks and high development costs at the outset, and, if successful, high payoffs in terms of employment and diversification over the long haul. Asian market economies, Ireland and many other countries which have been successful in diversifying on the basis of new industries have often done so with substantial government assistance at the outset. The key facet of such assistance is that small amounts of seed money early on can yield dividends in terms of employment, profits and government revenues once the initial hurdles are surmounted.

Part I: The Industries

1. Wild Food Mushrooms --The most valuable BC wild food mushroom export (almost entirely to Tokyo and Osaka) is our species of pine mushroom, *Tricholoma magnivelare.* No one to date has been able to culture pine mushrooms artificially to achieve levels of commercial production, but as the demand and *in-situ* cultivation technologies improve, both pines and mycomedicinals will be grown in dedicated cultivation forests, in mushroom plantations or in commercial agroforestry operations which seek to maximize both timber and pine mushroom production.

- X In an Aaverage-to-good” year such as 1996, around 392,000 kgs. of *T. magnivelare* were harvested in BC, but in a less-than-average year such as 1995, this figure falls to around 250,000 kgs.
- X The Pacific Northwest (BC, Washington and Oregon) supplies around 15% to 20% of the annual Japanese consumption of around 5,000 tonnes of pine mushrooms, which represent a luxury market (and a fall from the mid-1800s when the smaller population consumed around 12,000 tonnes annually.)

In the foreseeable future Japanese consumers will absorb all the pine mushrooms which BC can export; therefore, the limits to export become the limits of sustainable harvesting plus cultivation. These general market prognoses point toward:

- X intensive forest-based cultivation of pine mushroom areas to increase the export volume;
- X targeting forest types best suited to enhanced commercial yields (coastal and alpine stands of lodgepole pine);
- X implementing agroforestry projects in appropriate productive stands;
- X more extensive marketing and market research support for the private sector effort in Japan and the US.

A three tier market has arisen in Japan: Japanese pine mushrooms command the highest price; Korean pines fetch a half to a third of this price; and BC pines average a third to a half of the price of the South Korean imports. In 1997, a lower-than-normal year for prices, BC buyers selling to Japan reported prices of US $35/kg. on average for all grades, although at times prices spiked to US $95/kg. for the best grade.

One reason for the price differential between BC pines and those of Japan and Korea is that the latter are farmed in *cultivation forests* under stringent conditions including controls for insect infestation. Canadian pine mushrooms are attacked by several species of fly larvae and the resulting discard rate is a major factor in our lower prices.

Meanwhile, the Korean species are so devoid of flavour that they are sometimes injected with pine oil before being imported to Japan. Nevertheless Korean pines are worth more than Canadian because they look much like Japanese pine mushrooms. (Since Japanese consumers accept the Korean pines adulterated with pine oil, they might equally accept Canadian pines whose caps are stained with some organic substance such as soy to more resemble Japanese Matsutake).

Estimating the market value of naturally-occurring pine mushrooms vs. commercial timber in one area of the Nahatlatch watershed, we found that over a 120 year cycle, the value of the pines was about 17% of the market value of the timber. However if pine productivity were increased through the agroforestry technologies used in the Asian cultivation forests, over the same cycle the value of the pines rises to roughly twice that of timber.

To summarize current market activity:

- X there are sixteen active companies harvesting, buying or selling wild food mushrooms from BC, with over 90% of all exports by weight from Vancouver to Japan controlled by seven companies, six of which are Canadian.
- X In a good fruiting year for pines, these seven companies have before-tax revenues from pines and from other wild food mushrooms of approximately $45m but in a bad year this figure falls to around $25m.
- X Although over the past decade the BC pine harvest has approximately doubled, the average price paid to exporters has remained static - US $l9.00/lb to US $20.00/lb.

Other wild food mushrooms harvested in BC include: chanterelles (around 750,000 kgs. in a good year), boletes (l00,000 kgs.), morels (around 225,000 kgs.) and other species such as lobster, secondary boletes, cauliflower, hedgehog, and such (about 50,000 kgs. together). These other wild food mushrooms are generally sold in Europe, the US and other parts of Canada.

In the bolded items of figure 5, we have attempted to identify Abest bet" wild BC food mushrooms which could be harvested and exported to the US, Europe and Asia.

2. Wild Nutraceutical and Medicinal Mushrooms -- Dwarfing the markets for wild food-mushrooms, the 1997 world market for wild nutraceutical and medicinal mushrooms (and extracts and derived products) was US $l.3 billion.

BC is one of the world's most economically-valuable, environmentally-pristine sources of nutraceutical and medicinal mushrooms. These include:

(a) relatives of species used for centuries in Asia for treatment of specific illnesses and immune stimulation, and presently used in conventional Japanese medicine.
(b) other species being consumed by an aging North American boomer population to maintain good health.

Mainstream medical research in Japan, China and the Russian Far East indicates that polysaccharides, terpenes, steroids and other ingredients in many BC indigenous mushrooms have antibiotic, antitumour, and antiviral properties, reduce lipids in blood, stimulate the immune system, inhibit the synthesis of prostaglandins (hormones which regulate blood vessel size), extend the survival rates of patients with Hodgkins disease, lymphosarcoma and pancreatic cancer, and alleviate some side effects of AIDS.

Figure 8 highlights typical March 1998 prices for selected dried medicinal and nutraceutical mushrooms and mycelia extracts. To give an example of potential revenues: extracts from *Trametes versicolor*, a common BC fungal species, account for about 16% of Japan's national annual expenditures on anti-cancer agents, and one extract from this species sells in Tokyo for between US $1,500- US $2,000/kg.

Given that some US states are moving to regulate the amount of mycomedicinals harvested, and given the environmental catastrophes in Asia such as the 1997-1998 burning of Indonesian forests, prices will likely rise significantly over the next five years.
Figure 7 contains our first cut at identifying the most economically valuable indigenous medicinal and nutraceutical mushroom species upon which BC producers should concentrate. There are currently three BC companies selling mycomedicinals, all of which declined to discuss revenues.

3. Herbal Medicines and Nutraceuticals from Wild Plants B While pharmaceuticals are generally based on a single active ingredient, the therapeutic properties of herbal medicines arise from a synergistic combination of ingredients. With pharmaceuticals, companies may synthesize an active ingredient so that the source materials may no longer be needed; while with herbals, an entire plant extract is preferred and source material is always needed.

Until recently, large companies were not interested in researching *mixtures* because they could not be patented. In contrast, herbal medicines are typically sold as complex mixtures of several botanicals.

The main product differentiation among herbal medicines concerns:

(a) whether or not the product is organically produced, either through *wildcrafting* (foraging) or cultivation;
(b) standardisation of potency of ingredients.

Herbal medicines purified to certain stringent levels of standardised ingredients are called *phytopharmaceuticals.*

(i) World Markets and Regulation
The world market for herbal medicines (both crude extracts and phytopharmaceuticals) is around US $14 billion annually-- part of a larger market boom in which Americans alone spent over $27 billion in 1998 on alternative health treatments of all kinds. Not surprisingly, throughout the world, pharmaceutical multinationals are buying up producers of herbal medicines.
In Europe and especially Germany, there is:

X a sophisticated consumer pre-disposition toward botanicals;
X general acceptance of their use by doctors;
X prescription use of herbal medicines, with reimbursement of patients' expenses by health insurance;
X an open regulatory climate.

Herbal medicines are sold in the US as dietary supplements, meaning that producers do not have to finance expensive research to prove their products safe and effective; however, no claims can be made about the herbals as cures for illnesses. In Canada, herbals must still be sold as either foods (no health claims permitted) or drugs (and have to undergo clinical testing).

(ii) BC Wildcrafting (Gathering) Industry

The gathering of medicinal botanicals in BC is centered mainly in the Kootenays, the Slocan region and the Okanagan.

- In 1997, 15-20 serious commercial collectors (either through a company or under their own name) hired crews to gather medicinal herbs, with an estimated total of 200-300 commercial gatherers.
- These collectors of wild medicinal herbs sell almost exclusively to US bulk suppliers and large manufacturers of herbal medicines.
- Estimated 1997 gross revenues paid to these collectors were Can. $2m - $3m.
- gatherers are generally paid on a per pound basis and make around $100 per day.
- Premium prices are paid for produce which is organically grown or wildcrafted.

The main medicinal botanicals gathered from the wild in BC during 1997 (both in terms of revenues and weight) were:

-St. John's Wort (approximately l50,000 lbs)
-Oregon Grape (20,000 lbs.)
-Cedar Oil (around 6,000 lbs.)
-Devil's Club (less than 5,000 lbs.)

Medicinal botanicals wildcrafted in smaller quantities included Nettles, Burdock, Yarrow, Mullein, Arnica, Camomile, Tansy, Rose Hips, Cascara, Yew, lichens such as *Usnea wirthii*, and many others.

Indigenous medicinal BC plants much in demand on the European herbal markets include:

-Devil's Club (increasingly used as a ginseng substitute in herbal formulae)
-Cascara bark
-St. John's Wort
-Black Hawthorne (*Crataegus douglasii*)
-Mountain Ladyslipper (*Cypripedium montanum,* a threatened orchid taking fifteen years to grow)
-Hemp Dogbane (A*pocynum cannabinum*),
-*Valerian sitchensis*
-*Circaea alpina* (nightshade)
-*Equisetum pratense* (horsetail)

Other botanicals with rapid market growth include: Black and Blue Cohosh (threatened and growing in eastern Canada but not found in BC), Blood Root, and alder bark for its anti-oxidant compounds. 1997 prices for these and other BC indigenous botanicals are given in Figure 9. The US annual demand for St. John's Wort exploded from around 60 tons to several hundred thousand tons during 1997 after it was featured in a couple of national TV programs.

(iii) BC Manufacturers

In addition to the BC gatherers of wild medicinal botanicals, there are 50 manufacturers of nutraceuticals and medicinal herb products, most of which lack the technology and facilities for high quality, standardised production.

X In 1997 these companies employed l,710 persons and had around $60 million in sales of herbal preparations and dietary supplements, with an average annual growth rate of around 18% over the last two years.
X Generally, they use well-known species from the European pharmacopoeia and these companies are just beginning to diversify into indigenous BC botanicals. (No producers included indigenous medicinal or nutraceutical mushrooms in their formulae).
X Most manufacturers source ingredients from growers rather than wildcrafters and sell mainly into Canada and the US.

Although most BC herbal products manufacturers are deeply concerned with product quality and accuracy of standardisation claims, some will sell practically anything and in some instances concentration levels of ingredients do not match label claims, or an entirely different species from that claimed was sold.

There are presently six BC companies which can provide a certificate of analysis, test for contaminants or Afingerprint" samples using HPLC to compare an extract with others.

4. Pharmaceuticals from BC Flora and Fauna - There are two essential approaches to drug discovery: make them yourself, or borrow from nature. A drug may be developed by Arational design" in laboratories through techniques such as *combinatorial chemistry*; or researchers may look for models from nature through screening of wildlands-based fauna and flora. In both approaches a sophisticated technological capacity is required.

One way to borrow from nature is to ask first nations what they traditionally used for various illnesses. Such *ethnobotanical searching* is in competition with *automated masss screening techniques* developed to test huge numbers of candidate molecules created by *combinatorial chemistry.* Mass screening technology will soon be able to check tens of thousands of samples daily for bioactive molecules and it will soon be cheaper to screen everything instead of asking first nations elders about traditional use.

We were able to identify 22 firms in BC's pharmaceutical industry with 1997 revenues of around Can. $58 million and 930 employees. These firms produce human prescription drugs and human and veterinary non-prescription drugs, vitamins and nutraceutical supplements, vaccines and hormones.

X About a fifth of these companies have an in-house combinatorial chemistry capability (or access via their head office research facility).
X Seven of these companies, with l60 employees, are actively involved in natural products discovery, screening, clinical testing or production.

- X All the products of these seven companies were derived initially from BC indigenous wildlands substances.
- X Most of these seven companies-- such as Terragen Diversity Inc., Forbes Medi-Tech and Phytogen Life Sciences Inc.-- are UBC spinoffs.
- X Most of these emerging biotech spinoffs show annual losses. This is to be expected during their first few years of growth.

To generate revenues, these companies sometimes enter into collaborative agreements with pharmaceutical firms to screen their polygenomic libraries in surrogate hosts for bioactive compounds and receive licensing and milestone payments plus royalties. These smaller companies can innovate more effectively than large pharmaceuticals, but lack the financial and marketing clout to advance products through the regulatory and marketing hurdles.

5. Biocides (Non-Toxic Insecticides) and Biological Control Agents from BC Species-- In the rich life of a forest, many plants have devised innovative methods to fight insect pests. Most defensive chemicals in plants work through deterring insect feeding, the placing of eggs or inhibiting larval growth, rather than outright killing. In contrast, most synthetic insecticides poison insects' nervous systems-- but these organochlorines and pyrethroids act as poisons in humans too, leading to concerns about toxicity.

Alternate non-toxic insecticides (*biocides*) currently under investigation or on the market include behaviour-modifying substances such as pheromones, kairomones, repellents and anti-feedants; biorational insecticides such as growth regulators and chitin synthetase inhibitors, and other botanical insecticides. These emerging insecticides act very differently than conventional chemical insecticides, can target a single species, and require very low volume applications.

Lichens, leaves and roots of plants, fruit, dead insects, and many other organisms found in BC forests can be a fertile source of chemicals, fungi or bacteria which can aid in the battle against insect pests, fungal invasions and other plant diseases.

Another strategy is to introduce natural predators of pests to agricultural crops and forests. If the stock for these natural predators come from BC wildlands, then they are within the product definition of this study.

Often pharmaceuticals and biocides come from the same natural source material. To achieve efficiency of effort, insecticidal testing of BC natural sources should be piggybacked onto pharmaceutical testing of the same substances.

The US market for biocides is still only around US $250 million annually (compared with average annual US expenditures of US $10-$12 billion on pest-killing synthetic pesticides, and $32 billion throughout the world.) However, the world's biocide use is growing at over l4% annually, and at this rate will entirely replace synthetics within two and a half decades.

This sector in BC is comprised of nine firms:

- X four firms which raise biological control agents (insects that attack pests)
- X one phytodiagnostic firm
- X two firms concentrating on pheromones (B Phero Tech and a startup subsidiary of an Oregon Company, IPM Technologies Canada)
- X two pharmaceutical companies which also produce biocides.

There are also several US companies selling pheromone lure products in BC and several small, independent operators which produce pheromone products (for controlling coddling moths, for example.)

This industry employs approximately l50 people, had l997 collective revenues of around Can. $10-$12 million, and sells its products and services mainly in the US and Canada.

6. Anti-Phytovirals - The world market for substances that can effectively fight plant viruses in the field is an estimated US $10 - US $12 billion annually, and BC researchers are at the vanguard of the search for anti-viral compounds extracted from wildlands plants and fungi for the diagnosis and control of plant viral diseases. The BC research effort to identify naturally-occurring anti-phytovirals is currently concentrating on flavonoids, a large, diverse group of compounds found in all plant species except algae.

Presently the main commercial anti-phytoviral is a synthetic called ribaviran, which is mainly used to eliminate viruses from infected clonal breeding stocks. There are currently no practical, chemical controls for viral diseases of food crops in the field, and world estimated losses from plant viral diseases are approximately US $15 billion annually.

To date, few BC forest species have been examined as a source of inhibitors of plant viruses. But several phytocompounds have been identified which are partially effective in inhibiting viral diseases of commercial crops such as potatoes and fruiting trees, and it is expected that BC forests will yield additional substances. Such compounds would also benefit exporters who need to meet the phytosanitary specifications of importing countries. There are no BC companies currently producing anti-phytovirals. Of all the non-timber forest industries, this sector involves the highest risks in terms of product development, and largest potential short term payoff.

7. Ecotourism B Not just a trendy term, ecotourism is the most rapidly growing component of the world's tourism industry. AEcotourists" are interested in undisturbed nature, wildlife, traditional cultures, archaeology and conservation, and wish to be educated rather than merely entertained-- creating jobs for guides and tour operators.

Approximately l3,000 people were directly employed in BC's ecotourism industry in 1997, with estimated direct revenues of $l65m. If we include half of the revenues generated by our provincial parks plus annual amounts spent on outdoor accommodation, ecotourism was responsible for around $522m in annual provincial income in 1997. Using the models of Belize and Costa Rica, which have made ecotourism support an integral component of their industrial strategies, a wide variety of tax/fiscal incentives and programs could be put into place to accelerate this industry's growth.

As examples of recent expansion, in mid-1998, North America's largest fishing resort operator-- the Oak Bay Marine Group of Victoria with l,200 employees at eight resorts-- began buying BC lodges to convert them to ecotourism destinations; and Roots (the "environmental" shoe company) is setting up ecotourism lodges on Vancouver Island. Of all the products and services discussed, ecotourism has the greatest potential to bring significant revenues into impoverished first nations communities.

8. Floral Greenery B This sector has two parts in BC: four companies which sell directly to European buyers, and l8 smaller firms which sell to US buyers who in turn sell into Europe. Direct sellers get better prices.

The main product in terms of weight is salal, and ferns, cedar boughs, huckleberry, boxwood and other floral greenery are regularly harvested in BC and sold to Europe, the US, Japan and the distribution centre of Hong Kong. Some floral greenery companies also harvest wild food mushrooms, but they do not take medicinal botanicals, which is a separate industry.

The approximately 22 firms in this sector had 1997 collective gross revenues of between Can. $55m - $60m. The largest firm had 1997 revenues of between $6m-$8m and several firms had 1997 revenues of around $2m. The total number of commercial pickers in 1997 was around l3,000.

Part II: The Economic Strategy

A major opportunity awaits any BC government that will act with determination to rebuild our forest industry on a new and more varied basis. Though dwarfed by the giant timber industry, the non-timber forest industries highlighted above employed almost 32,000 people in BC on a seasonal or full-time basis in 1997 and had direct corporate revenues of $280m and provincial revenues in excess of Can. $630m.

These figures do not include revenues from native plants taken for rehabilitation, restoration and ornamental purposes, revenues from BC's manufacturers of herbal medicines and food supplements (since they presently use so few indigenous ingredients), or sales of essential oils used in perfumery and aromatherapy B all significant growth areas.

The annual corporate revenue growth of these industries over the past three years varies widely, ranging from yearly averages of around 10%-12% for some of the wild food mushrooms to over 30% for several nutraceutical manufacturers.

It has become common wisdom that BC is overly dependent on resource-based industries (which generate in excess of three quarters of total merchandise exports), and that economic diversification is needed urgently. *We are suggesting that BC become even more dependent on resources for export earnings,* through aggressively supporting these emerging industries.

These forest resources are not our Adependence": they are our *comparative advantage.* Some of these industries use advanced technologies, some are low-tech-- this does not matter, because most gather or manufacture *comparative advantage products* from BC and the Pacific Northwest which are found nowhere else. To date, FRBC has supported few of the value-added product areas described in this work.

Properly supported, these revenues could increase by a factor of 8-10 during the next decade to comprise in excess of a third of total forest-derived revenues (as computed at pre-recession prices.)

Thus far we have developed a limited number of forest products, mainly timber and pulp. But judging from countries like Malaysia and Laos-- over the next decade there will be an explosion of new products from BC forests:

- medicinal and food mushrooms, and phytopharmaceuticals for humans and animals;
- preventative healthcare products such as the tsunami of nutraceuticals coming onto the US market;
- resins, gums and camphors, essential oils and other cosmetic substances such as bases for face cream, perfumes, sunscreens and hair tonics;
- genetic material for foodstuffs, biocides, natural medicinal bases, new dental products, spermicides and non-toxic contraceptives;
- anti-viral agents for plant diseases;
- crop protectors such as insect exudates which repel birds;
- chemical "detoxifiers" for both industrial processes and human tissue;
- new building materials modeled on naturally-occurring forms and structures.

People will always need to build wood houses and use paper for documents; but timber and pulp will be only two forest products among a myriad group. Meanwhile, ecotourism in BC forests will continue to grow. Thus our economic strategy has two parts:

> -strengthening the international competitiveness of our traditional forest industries, (mainly through smarter tree growing on a smaller land base);
> -simultaneously facilitating, through tax support, agroforestry practices and cultivation forests, the emergence of these new industries based on ingredients in under-story plants, lichens, insects, bark, soil organisms, fungi, waste, and other flora and fauna.

In the following sections, we first present sectoral strategic measures, and then general tax/fiscal incentives to be applied to all the industries analyzed above.

A. Sectoral Measures

1. Increased Production of Pine Mushrooms - Given the growth potential for pine mushrooms from BC, the underdeveloped state of the industry, a continuing strong price in spite of the Japanese recession and an expanding market in the US, *the provincial government should move aggressively to economically develop the pine mushroom resource*.

Provincial government policies can increase both the demand for, and supply of, BC's premium wild food mushroom, *T. magnivelare,* by addressing product quality, export volumes, product price and market size.

Measures to increase volume and productivity include:

X gradually establishing mushroom cultivation forests;
X extending the areas where pine mushrooms fruit;
X adapting technologies prevalent in the cultivation forests of Japan, China and South Korea.

2. Asian Cultivation Techniques - Asia's cultivation forests for pine and other mushrooms offer successful commercial models, technologies and techniques which can be adapted to improve the quality and quantity of BC's pine and mycomedicinal harvest. Cultivation techniques include:

-cutting shrubs and selected trees as a forest ages for aeration and sunlight on the forest floor;
-changing the litter thickness and adding wood pulp waste, artificial irrigation tunnels or small plastic hoods over colonies of pines (called *shiros*) to control soil humidity and temperature;
-pest control, fertilization and a host of other technologies to entice more pine production *in-situ.*

We therefore suggest that:

X The provincial government should direct its chief mycological expert to assemble a team to conduct adaptive research tours of the cultivation forests and pine mushroom research facilities in Japan, China and South Korea.
X With findings from these tours, the government should publish an initial simple language document aimed at buyers, exporters, growers, pickers, and new ventures describing the techniques and technologies successfully used with related species in Asia and associated productivity gains, the applicability of these techniques for BC conditions and species, and specific agricultural techniques to maximize pine production here.
X The Ministry of Forests should then initiate a program of adaptive research designed to increase pine mushroom production in BC and contract much of it out to the private sector and research institutions.

3. Cultivation Forests for Pines and Mycomedicinals - Cultivation forests dedicated specifically to enhancing in-situ growth of mycomedicinals and *T. magnivelare* should be introduced into the present forest tenure system.

In order for these lucrative mushroom industries to flourish, they must be given recognition in overall forestry planning and the forest tenure system.

X The government should introduce on a gradual basis, both cultivation forests exclusively dedicated to pine mushrooms and those dedicated to the joint maximization of pines, timber and mycomedicinals.

X These cultivation forests should be made commercially available, under a variety of arrangements, (including competitive bidding) to a wide number of concerns Branging from the private sector to community forest projects. A special arms-length body should be set up to administer the handling of rights at below-market prices.

Custodial harvesting rights can be assigned for an extractive reserve for single or multiple resources. If cultivation forests are rented only to companies with the financial resources to develop these and with the objective of maximizing governmental Astemage" fees, wildcrafters and rural people will not get leases and will be excluded. Since it is part of provincial policy to diversify poor rural economies in BC, below-cost leases for some of the cultivation forests should be reserved for local small businesses, community forest groups and special forest products cooperatives, which should be supported through a variety of means. Coops can encourage entrepreneurship at the local level.

4. Research on Sustainable Harvests - As we still do not have the most basic information about quantities of pine mushrooms or mycomedicinals growing in BC, research is necessary to create baseline estimates of fruiting to ensure that harvests are sustainable. These adaptive research areas hold the greatest short-term potential for new jobs and products.

5. Promotion of BC Pine Mushrooms in Japan - The provincial government should increase Japanese consumer awareness of BC pine mushrooms. A provincially-funded exhibition of industry participants touring four or five smaller Japanese cities would receive extensive media coverage and be well-attended. This should be repeated about every four to five years.

6. Introduction of "Stemage" - If cultivation forests for pine mushrooms are to be made available to the private sector through a variety of arrangements, we must rethink forest land tenure and introduce the notion of *stemage* -- the forest botanical equivalent of stumpage: a small amount paid to the provincial government per unit of forest botanical gathered from Crown land. Eventually it will be appropriate to set up a system for botanical stemage, but given the nascent nature of the non-timber industries, the government should forego such revenues for a decade or more.

7. License Buyers of Pines - The 1995 recommendation of the Pine Mushroom Task Force, that buyers of pines from crown lands be licensed, should be immediately implemented. A fee should be charged to purchase the license with appropriate fines for non-compliance, and a condition of licensing should be the bi-weekly provision of information about: the species bought; date of purchase; weight and grade purchased; price paid per grade, and the buying station location. Most buyers keep this type of information anyway, and to lessen the data burden, this information could be summarized. Given the potential value of pine mushrooms to BC, data on the gathering and sales should be tracked. There is currently no way to obtain even approximate data. As the problems in this system are ironed out, licensing of buyers should be gradually extended to other botanicals.

8. Support Local Processing and Preparation Facilities - The provincial government, through its agricultural and technology support programs, should help the private sector to build pine mushroom processing and preparation facilities near some of the prolific gathering areas, starting with the north-west region.

The lack of such facilities both inhibits growth and drains away employment opportunities. For example, a major factor limiting growth of the Nass region industry is the absence of proper processing facilities. Since much of the gathering is done by transient efforts of large Vancouver-based companies, most wealth produced by the industry leaves the community, and northern businesses are not able to generate jobs.

Both primary and secondary processing of pine mushrooms can be done locally, with job opportunities for local communities and first nations.

Benefits include:

X better-paying jobs and value-added employment in poor regional economies. (Harvesting is often seasonal, low-paying and devoid of benefits; better jobs exist in processing and marketing the mushrooms.)
X greater efficiency, if activities such as eliminating infested produce, processing for specific orders, and preparing shipments for delivery are done locally.
X time savings. Local processing could shave half a day off of the transition time to Japan and enhance product freshness, a major price factor.

If the infrastructure for pine mushroom processing also included mycomedicinals, new job sources could be created for small communities in several parts of the province.

9. Promote BC Mycomedicinals - Several of our Canadian mycomedicinals -- such as *Ganoderma applanatum* and *G. tsugae* -- contain therapeutic ingredients that resemble those of such Asian high-volume sellers as *Ganoderma lucidum* (AReishi"). Our species could therefore be promoted world-wide as the BC AReishi".

The government should fund laboratory analysis of the ganoderic acids, triterpenes, polysaccharides and other ingredients in selected BC medicinal and nutraceutical mushrooms, and, to promote consumer awareness, popularize the results.

10. Map the Other Botanicals - Starting with St. John's Wort, Oregon Grape, Cascara, Devil's Club, and commercially-valuable plants near extinction, the government should document and map locations of the species of Figure 9, and make informed estimates of the amounts of each species growing.

With these species, we also need to know their biological productivity, their reactions to harvesting techniques, and the best harvest practices with respect to timing and optimal sustainable levels.

11. Research the Efficacy of BC Botanicals - Faced with a bewildering array of medicinal and nutraceutical products, consumers constantly seek research results to guide their choices.

To increase demand for BC products, the provincial government should try to direct appropriate federal funds toward research on the efficacy of BC wildlands-based medicinal and nutraceutical botanicals-- in particular some of those used by first nations.

Based on proper research, for example, it may be possible to establish a significant US and Asian market for BC Devil's Club as a wild ginseng substitute (with government promotion and market development.) The Saskatchewan government has recently invested $1m in promoting their nutraceutical industry.

12. Allow Wildcrafters Access to Waste - Since so many emerging non-timber products come from the *waste* of traditional forest industries such as bark and tall oil, the government should expand wildcrafters' access to this waste. Measures would include: use of appropriate logging roads, and working with timber tenure holders and other waste sources so that wildcrafters may access understory plants *before* any clearcutting, and wastage afterwards.

13. Investment Partnership Board - A recent BC business summit proposed that the provincial government work with the business community and other stakeholders to set up an *investment partnership board* which would market BC internationally as an attractive business location. One area of emphasis of this board should be the emerging non-timber forest sectors with high annual growth rates B nutraceuticals, phytopharmaceuticals, herbal botanicals , mycomedicinals, biocides and ecotourism.

14. Encouragement of Agroforestry - Currently certain BC legislation and policies discourage agroforestry. Many agroforestry products are not recognized as agricultural crops by the BC Assessment Authority's Land Classification/Taxation scheme and hence do not receive lower agricultural land tax rates. Also, some of the rules of the Agriculture Land Commission and the Forest Land Commission are prejudicial against agroforestry efforts. Adequately addressing agroforestry concerns in the tax structure requires a more subtle approach than the traditional split between forestry and agriculture.

X The provincial government should therefore conduct a tax review of these matters, first determining which of BC's existing agricultural programs and incentives should also apply to agroforestry operations.
X This review should also consider tax/fiscal mechanisms from other countries and regions of Canada used to preserve, consolidate or extend farmland, which could be modified to include land utilized for agroforestry.

The inclusion of agroforestry businesses in any BC legislation will involve revising the classificatory scheme for property in BC, an extended definition of Class 7, AManaged Forest Land", a more extensive application of the Split Classification, a revision of the assessment procedures and criteria, and revision of BC Reg. 411/95, AStandards for the Classification of Land as a Farm".

The main objectives are:

X to revise the existing farm property tax concessions to apply to agroforestry production and cultivation forests; and
X to accelerate the permanent or term classification of privately-held lands into designated cultivation forests.

15. Liberalized Regulations for Natural Health Products - In November l998 the federal Standing Committee on Health tabled ANatural Health Products: A New Vision," with recommendations for liberalized sales of natural health products. To date, however, none of these recommendations have been passed into law. Natural health products classified as foods still cannot make health claims in either packaging or marketing. Products which do make health claims have to be regulated as drugs. This involves the provision of very expensive monographs or controlled clinical trials to obtain a Drug Identification Number-- an obstacle that stops many product developments. Meanwhile, Canadian manufacturers of natural health products remain at a market disadvantage compared to producers in other countries.

This legislation proposed by the Standing Committee on Health is a good first step toward improvement. Powerful vested interests oppose such legislation, making it important that, as the major Canadian source of medicinal and nutraceutical wildlands substances, BC lobby for its rapid passage into law.

16. Liberalized Licensing for Biocides - Just as regulation is hindering the development of natural health products, the regulatory protocols of Canada's Pest Management Regulatory Agency are stifling the biocide industry in Canada, and the concepts in which existing regulations are written, are not remotely applicable to biocides, which often contain a gamut of ingredients acting in a synergistic manner. As the major source of natural biocides in Canada, BC should lobby for an in-depth review and liberalisation of licensing criteria.

B. Fiscal Incentives and First Nations' Rights

The heart of any economic strategy lies in the tax/fiscal incentives given to industry.
In the following we first present general taxation recommendations which would apply to all sectors of the BC economy, and facilitate a more level playing field with competitor countries. Subsequently, measures are proposed specifically for emerging non-timber forest industries.

17. Sales Tax of Research Equipment -To increase BC's competitiveness with other countries and regions of Canada, we recommend that the government exempt the provincial social services (sales) tax on all machinery and production equipment used for research, non-routine testing and analysis, or new manufacturing startups. (The goal is to encourage companies to adopt new and more efficient production technology. If the recipient is a manufacturer, this incentive should be structured so that exempted equipment can be used for a combination of research and manufacturing).
18. R&D Tax Credits - Since R&D is so important to all the new industries on which the province's continued economic dynamism depends – including non-timber forest products - it is important that BC at least match the support given by other provinces to product research. We thus recommend that:

- the provincial government put into place a l0% tax credit on R&D, paralleling the other provinces;
- These credits should be refundable in the same way the federal credits are and to the same type of recipients, Canadian-controlled private corporations (CCPCs);
- as with the federal R&D incentive, the refundable portion should be capped at $2 million of eligible R&D expenditures and available only to CCPCs. The non-refundable portion should not be capped.

While a l0% tax credit on R&D is relatively modest, it will signal the private sector that BC recognizes the role of private research in economic growth.

19. Deduction for Technology Transfer - We recommend that BC offer a 100 percent deduction (capped at $20 million annually) for a company's arms-length purchase of qualifying intellectual property such as licenses, permits, patents and know-how. This deduction will support technology transfer from offshore.

20. Tax Credit for Payments to Research Institutions - We recommend that BC offer a tax credit which can refund to companies 20% of a maximum amount of $20 million in qualifying expenditures on R&D carried out on a contract basis at post-secondary educational institutions, non-profit research organizations, and research facilities associated with hospitals.

21. Taxation of Foreign Researchers - Any company currently producing phytopharmaceuticals and nutraceuticals has to cope with shortages of knowledgeable business managers and skilled people to bring products to markets. There is also a lack of professionals who can manage the diversity of activities involved in clinical trials and regulatory procedures. It is also difficult to find experienced lawyers who can beneficially structure partnerships and intellectual property agreements.

Although we cannot match US largess, provincial policies should not have the effect of making BC a less favourable place to locate new ventures than other Canadian provinces. For several years Quebec has offered a very successful three year, renewable, provincial tax holiday on salaries and stipends paid to foreign researchers by Canadian companies, including legal research pertaining to intellectual property and regulatory procedures. We should do the same.

22. Corporate Tax Holiday

To encourage these emerging industries, we recommend a five year corporate tax holiday for:

- Canadian-controlled companies cultivating or manufacturing pharmaceuticals, nutraceuticals and other natural health products or ingredients from BC wildlands sources;
- producers of antiphytovirals, mycomedicinals, wild food mushrooms, and essential oils from the same sources;
- the six or seven companies which provide technical services to these sectors;
- ecotourism companies.
- If this measure becomes actionable under NAFTA and WTO rules, (which we doubt), the same effects can be achieved through the mechanism of enterprise zones.

23. Export and Pioneer Incentives - If the notion of a tax holiday on selected industries is not amenable to provincial policy makers, we recommend that the following combination of incentives be granted to these industries:

- an export incentive which grants a 90% tax exemption on all profits above a specified base of export sales. This incentive should be granted for three or five years, with the longer period being given to companies which do not qualify for pioneer status, below.

- a pioneer status incentive, which allows tax exemptions of 40% of corporate income tax for five years if they undertake new manufacturing activities in BC in these sectors.

As most of the existing acceptable language of taxation policy was written in a time when Amanufacturing" meant smokestacks and factories, it must be understood that in the present day Amanufacturing" also includes enhanced growing techniques in agroforestry operations such as cultivation forests. If the latter alternative is chosen, ecotourism operations should still receive a corporate tax holiday. These incentives plus the traditional knowledge fund suggested below will cost the provincial government approximately $94 m annually in deferred revenues, but with a five year perspective, government is a net tax beneficiary.

24. First Nations Traditional Knowledge Fund - To create a stable and confident business climate for the economic development of these non-timber forest resources, we must also settle with first nations peoples and include them centrally in these developments. This involves dealing in an efficient and fair manner with both land claims and *traditional knowledge.*

Three problems arise:

- X How should the province deal with commercially-useful traditional knowledge taken in the past?
- X What should be done to ensure that first nations have appropriate control over their (undisclosed) traditional knowledge in the present, and financially benefit from its commercializations when they wish to?
- X And how can the province help perpetuate a rapidly disappearing body of first nations knowledge about the uses of BC fauna and flora B knowledge which is providing the commercial basis for a variety of twenty first century health care products?

In BC, if we consider just the recording of the names of first nations' medicinal plants and their associated illnesses, approximately twenty five to thirty percent of the entire knowledge base has passed into the public domain through the publications of ethnobotanists and other academics. This means that a great body of knowledge is still privately or collectively held by first nations.

Beyond its spiritual value to aboriginal peoples, this knowledge base is a commercial resource both for first nations and for those who form joint ventures with them. This knowledge base is evanescing rapidly with the death of the elders.

Generally herbal dietary supplements, nutraceuticals and other health care products, rather than pharmaceuticals, will emerge from this knowledge base and be commercialized. Due to recent advances in computerized high-throughput screening, big pharmaceutical firms will soon find it cheaper to randomly test everything they can collect (as they did at first) rather than ask elders. When this happens, they will generally stop looking for pharmaceuticals in the traditional knowledge base of indigenous peoples..

The province should therefore set up a *traditional knowledge fund*, used to pay annual honoraria directly to first nations elders knowledgeable in the medicinal and nutraceutical uses of fauna and flora to continue their regular work. Each of BC's 191 bands has at least one main person with such knowledge, well-recognized by the community. These people, often impoverished, have difficulty recruiting apprentices among first nations youths who have lost interest in this knowledge. This fund should also directly pay first nations apprentices a salary to absorb this knowledge. All of this must be done on a non-disclosure basis to be workable.

25. Economic Benefits for First Nations - At the same time, much can be done to ensure aboriginal control of, and financial benefit from, undisclosed traditional knowledge; and it is in the government's interest to achieve these goals for stable business development. Thus the provincial government should draft and enact basic access legislation which:

- X recognizes first nations as owners of traditional knowledge and practices concerning the uses of fauna and flora on their traditional territories;

- X obligates parties seeking commercially useful traditional knowledge from first nations peoples, or bioprospecting on traditionally-held territories to fully inform local communities about their project and to seek their *prior informed consent*. (Such informing should include the project's objectives, where it will take place, species sought, quantities to be harvested, duration, nature of product, anticipated markets and sales, and related information);

- X specifies that these parties share direct fiscal benefits with first nations-- that is, give fair and equitable compensation-- when a project results in commercialization(s). Benefits could take the form of royalties, material transfer fees, contributions to capacity building, and other forms.

26. Sample Deposits - Legislation should also require all bioprospectors to deposit duplicate samples of BC biological resources in a designated *ex-situ* herbarium. Exchanges between first nation communities (of biological resources or traditional knowledge) would be exempt in the legislation. Throughout the world and in other parts of Canada there is equivalent emerging legislation which, if properly modified, could serve as a model for BC. Progressive BC legislation would contribute to a stable business environment.

27. Set Up a Working Group - These incentives and strategic measures are not exhaustive. The provincial government should therefore set up a working group, with representatives from government, the private sector, first nations and other stakeholders, to fine tune and extend such measures and to conceive a detailed plan to develop the non-timber forest products and services, which will be a mainstay of the BC forest economy in the next century.

Part I. The Industries

Introduction

Part I. presents economic and industrial analysis of some non-timber forest products (NTFPs) and services in BC -- wild food, medicinal and nutraceutical mushrooms; floral greenery; pharmaceuticals and nutraceuticals from plants, bark, lichens and soil organisms; biocides (non-toxic insecticides) from the same sources; anti-phytovirals (medicines *for* plants), and ecotourism.

In Part I we have attempted to identify BC's most economically valuable non-timber forest products and services. These results are part of an FRBC-funded study to conceive an economic strategy to support the development of these emerging products and services in BC. This strategy is presented in Part II.

This study was conducted by a research team from Cognetics International Research Inc., Creekside Resources Inc., (the business arm of the Mount Currie Band), and the Centre for Asian Legal Studies, Faculty of Law, UBC.

One of BC's comparative advantages lies in the diversity of emerging forest products and services, some of which are based on *bioprospecting*. This search for fauna and flora whose underlying genetic and chemical information is providing the basis for new forest products—is now part of the industrial strategies of several countries, and these products range from biocides, anti-phytovirals, medicinal and nutraceutical fungi, non-toxic contraceptives; birth facilitators; high-end oils, dyes and damars; agro-chemicals; herbal botanicals; preventative healthcare products such as sunscreens; bio-detoxifiers of both human tissue and industrial processes, essential oils and crop protectors, to pharmaceuticals from plants, lichens, bark, wood waste and soil organisms. Some of the enabling technologies (not well-developed in BC's private sector) involve recent advances in computer-automated enzyme and receptor screening and related means of natural products testing plus combinatorial chemistry.

At the same time there are real economic possibilities to extend markets for NTFPs which are presently just gathered from the forest such as food mushrooms, floral greenery, and native plants. Given these developments, we have tried to:

1) review successful international producers of NTFPs and services—their main products, revenues, profits, exports, and technology strategies;
2) identify current BC producer and user firms and organizations of NTFPs and services and relevant industry-level economic data—products, revenues, revenue growth, employment, exports, export barriers, etc.;
3) identify the BC industrial capacity to perform natural products testing and discovery;
4) review and analyze the world markets for selected BC NTFPs and services and identify new products, services and markets based on BC wildlands substances, not currently being produced,

which forestry, biotech, and other new entrants could produce and export;

5) formulate an economic/technology strategy to support the development of NTFPs and services in BC, including tax and fiscal incentives and programs, technology sourcing measures, legislative analysis pertaining to first nations' property rights to fauna and flora and to traditional knowledge of their uses, specialized technology support measures, and a commercial tenure framework for development.

A specific product category which emerges in this work across several sectors is that of *nutraceutical*. If a medicine is something one takes when sick to get better, a nutraceutical is something one eats when one is healthy to stay healthy or get healthier. Nutraceuticals may be preventatives. It is now known, for example, that foods containing folic acid reduce neural tube defects in a developing fetus and that fibre-enriched foods are linked to lowering the risk of developing colon cancer. Food products and herbal supplements that contain ingredients and additives which yield therapeutic benefits in addition to nutritional benefits have estimated global sales of between US $l0-$12 billion worldwide in l998 (Chatfield Dean & Co. undated), and nutraceuticals can now be bought which inhibit the uptake of cholesterol, manage hypertension, curb free radicals which cause cancer and reduce risk of cardiovascular diseases. All of these nutraceuticals come from natural sources. Many of those nutraceuticals growing into favour in the US markets are found on BC wildlands.

I. Floral Greenery

Since the Forest Practices Branch of the Ministry of Forestry recently commissioned and completed a study of floral greenery (Westland Resource Group l998), we are not examining the floral greenery sector in detail in this work and have focused on the following NTFP sectors –wild food, nutraceutical and medicinal mushrooms (also called mycomedicinals), wildcrafting of medicinal botanicals; anti-phytovirals; biocides; and medicines from vascular plants, insects, lichens and soil organisms.

Nevertheless given its potential for growth, we have ascertained the following estimates about the size and structure of the floral greenery industry in BC. We were able to identify twenty two firms in this sector, with collective gross revenues in l997 of between Can. $55 and $60 million. The largest firm had l997 revenues of between $6-$8 million and several firms had l997 gross revenues of around $2 million. The total number of persons commercially picking floral greenery during l997 is estimated at between twelve to fifteen thousand.

This sector is comprised of two parts –four firms which sell directly to Europe, and l8 smaller firms which sell to US buyers who in turn sell to European buyers. The direct sellers get better prices. For example with the main product in terms of weight)—salal-- the smaller firms selling to US concerns pay pickers Can. $l.80/bunch, (a bunch is l.2 pounds), and sell to US buyers who drive to BC at $2.10/bunch. They thus make 30 cents/bunch. The firms which sell directly to Europe, although they must pay transportation costs, receive 30 cents/bunch plus a mark up of between 20%-30% (Richard Ross personal communication).

In addition to salal, (75-80% of the BC floral greenery business in terms of sales), ferns, cedar boughs, huckleberry, boxwood and other floral greenery are regularly harvested in BC and sold mainly to

Europe, Japan and eastern Canada. Some floral greenery companies also harvest wild mushrooms, but they do not take medicinal botanicals, which is a separate, small industry subsequently described.

II. Ecotourism in BC

Still another non-timber forest service which we are not scrutinizing in detail is ecotourism. With the growth of environmental sensitivity worldwide, a new type of tourist has begun to appear in tourism marketing studies and charts. Such “ecotravellers” are interested in nature, wildlife, traditional cultures, archaeology and conservation concerns. They wish to be educated rather than amused, informed rather than entertained. In developing world ecotourism, they like to believe that they are helping just by being there, and a growing trend is that of ecotourists paying for the privilege of offering their labour – building paths in the Monte Verde rainforest of Costa Rica, or participating in archaeological digs, or tree planting to prevent river erosion.

Ecotourists have always been around, but now there are more of them and they have more money.

With comparatively little financial or policy help from the provincial government, BC is already a world ecotourism destination, and this sector is the fastest-growing component of the world’s tourism industry (twelve percent annually). Properly developed ecotourism destinations and activities also hold the greatest promise of all the non-timber forest products and services, to bring significant revenues into local first nations communities. Information-intensive activities are the most rapidly growing part of ecotourism worldwide and are ill-developed in BC. To give but one example, Whistler tourists would pay considerable monies to tour, with an informed guide, the petroglyphs in the Mount Curry area.

Approximately l3,000 persons are directly employed in BC’s ecotourism industry (R. Harris, Tourism BC, personal communication), with estimated l997 direct revenues of Can. $l65 million. If one adds half of the Can. $454 million annually generated by our provincial parks plus an annual Can. $l32 million spent annually on outdoor accommodation, ecotourists annually are responsible for approximately Can. $522 million in provincial income. This amount dwarfs the current provincial and private revenues from the other NTFPs and services, and this sector merits further study and significantly increased government support. Using the model of Belize and other countries which have made ecotourism support an integral component of their industrial strategy, there is a wide variety of tax/fiscal incentives and programs which could be put into place to help this industry grow. In mid-l998, North America’s largest fishing resort operator, the Oak Bay Marine Group of Victoria, with 1,200 employees at eight resorts, began purchasing BC lodges to convert them to ecotourism destinations, and Roots (the “environmental shoe company”) is also planning to set up ecotourism lodges on Vancouver Island.

With this cursory review of BC’s floral greenery and ecotourism industries, we turn to the main body of this work with an examination of BC’s gatherers, buyers and exporters of wild food mushrooms.

III. Wild Food Mushrooms

Introduction

Many wild forest mushrooms are commercially harvested in BC. The most valuable of these are typically ectomycorrhizal such as the pine mushroom, (*Tricholoma magnivelare),* chanterelles, boletes, truffles and hedgehogs. At the present time truffles are the only ectomycorrhizal food fungus which is in widespread cultivation in the Pacific Northwest (only in Washington and Oregon states).

The most valuable wild food mushroom crop, pines, is not yet a cultured and tended food crop in managed forests in BC or the US as it is in Japan and Korea, but as the demand and cultivation technologies get better, both pines and other species also will be grown in dedicated cultivation forests, in mushroom plantations or in commercial agroforestry operations producing mycomedicinals, pines, and timber. Agroforestry, the *in-situ* cultivation of several floral or faunal species in the forest, is really just beginning in BC and this effort has been spearheaded over the years by R. Hallman (l998) of the Creston division of the Ministry of Agriculture, Fisheries and Food.

Ectomycorrhizal fungi form an integral relationship with trees, wrapping themselves around tree roots and permeating some of the cells in the tree's tiny feeder roots to form a mycorrhiza organ. Such facilitates the passing of nutrients from the soil into the tree. In reward, the fungi absorbs organic compounds necessary for survival from the trees' photosynthesis process. These fungi also connect differing tree species and allow, for example, the passing of nutrients from (what were previously thought of as) "junk" trees to valuable timber species.

However the actual impact of harvesting wild mushrooms is difficult to measure. Since the bulk of the fungi is underground and the mushroom is merely its fruit, mycologists cannot determine if 2% or 90% of all the mushrooms of a certain species in BC are being picked. Many harvesters, on the other hand, claim that picking mushrooms stimulates productivity. However, destructive harvesting techniques (such as raking) may destroy the body of the fungus which is typically found in the top layer of the soil. Despite this it would seem that as long as the underground portion of fungi remain intact and the variety of surrounding trees feeding fungi nutrients are also intact, mushrooms can be picked every year.

Pine Harvests and Exports

The most valuable BC wild food mushroom export (almost entirely to Tokyo and Osaka) is (*Tricholoma magnivelare* (Peck) Redhead) - a species of pine mushroom. There are at least four commercial species of *Tricholoma* in the world – *T. matsutake,* the most economically valuable species of East Asia; *T. bakamatsutake,* also from East Asia; *T. magnivelare* of North America, and *T. caligatum* from North Africa, Eurasia and North America. In addition to other (non-commercial) *Tricholoma* species, BC has both limited numbers of *caligatum* and *magnivelare* in profusion.

A small quantity of BC pine mushrooms is exported also to South Korea, and just as Canadian buyers are active in Washington and Oregon states, US buyers purchase in BC. K. Blatner (personal communication) found that 21% of all processed pine mushrooms from the US Pacific Northwest are first exported to Canada and sold in Japan. Data taken during this research would indicate the Canadian purchases of US fresh pines which are exported to Japan as a Canadian product comprise about 25%, on average, of the BC harvest of pine mushrooms. Canadian trade data does not mirror these cross-border transactions.

In some years, the entire Pacific Northwest share of the pine mushroom market in Japan has exceeded

20% but comprised an average of l6% for l991-l995 (Weigand, 1997).

In an “average-to-good” year such as l996, approximately 392,000 kgs. of *T. magnivelare* were harvested in BC. In a less than average year such as l995, this figure falls to around 250,000 kgs. Most of this product is exported from Vancouver within three days to Japan, where it is consumed almost entirely in the two cities mentioned above. In most of Japan, consumers do not even know that Canada produces pine mushrooms. In October l998, a Canadian company exported pines directly to Sapporo for the first time and local and national Japanese TV extensively covered this novel media event.

Japanese imports of different species of pine mushrooms (all called Matsutake in this data , by year, by source country and by quantity are given in Figure l. for the period January l, l995 through September 30, l997 (Source: Canadian Embassy Tokyo).

Figure 1. Japanese Imports of Matsutake, Tariff Classification No. 070951919, by Year, Kilograms Imported and Country of Origin
(source: Canadian Embassy in Tokyo)

	1995	1996	Jan.- Sept. 1997
R. Korea	632,927	169,561	67,473
S. Korea	1,141,071	540,618	531,887
China	1,191,078	1,152,220	980,763
Lao PDR			224
Bhutan	1,747	3,299	2,758
Bahrain	223		
France	200		
Turkey	3,936	43,813	
Canada	339,990	509,857	155,144
USA	1,631,195	172,413	71,571
Mexico	46,033	23,267	7,771
Morocco	828	85,845	
Algeria	181		
Australia	3,720		
Total	4,993,129	2,700,893	1,817,591

Our BC harvest estimates for pine mushrooms in l995 and l996 were derived in two ways: first method: several buyers and mycologists were asked to estimate the percentage of total BC harvest of pines represented by the northwest region—that is, the Nass valley and surrounding regions. This area includes Terrace, Thornhill, Cedarvale, Kitwanga, Kitwancool, Skeenna Crossing, the Hazeltons, Kispiox, Cranberry Junction, Miziadan Junction, Steward and Highway 37 North to Dease Lake and east to the Smithers/Huston areas. It was then ascertained that all but two buyer companies air shipped this product first to Vancouver and then to Japan, and air freight information was obtained from the Terrace, Smithers and Prince George airports on weights of *Tricholoma* shipped during the l995 harvest season. This amount was then added to the tonnage of the two other companies and extrapolated to the entire provincial harvest using the average percentage (60%) of total harvest represented by the area as estimated by the mycologists and buyers in that region. This method involves some assumptions which may not be accurate but yields a realistic order of magnitude estimate -– 254,000 kgs. harvested in BC in l995, a "below average" year for *T magnivelare* fruiting.

second method: working from the other end, data was obtained from the Canadian Embassy in Tokyo on Japanese imports of Canadian pine mushrooms for the period of January l995 through September l997 --including kilograms imported by year, and import values in '000 yen and yen/kg. For example in l995 Japan imported 339,990 kgs. of *T. magnivelare* from Canada valued at l,506,ll5,000 yen and in l996 (a "good-to-average" fruiting year), imported 509,857 kg valued at 2,690,36l,000 yen. (This last figure does not represent the retail or wholesale auction prices in Tokyo or Osaka but is an assigned import value based on weighted grades). Conservatively assuming that (a) BC produces around 95% of all *Tricholoma* harvested in Canada and exported to Japan, (b) that *Tricholoma* imported from the US to Vancouver and resold in Japan as a Canadian product represents around 25% of the BC harvest, and © that local consumption is negligible, this method yields a yearly BC harvest of pine mushrooms for l995 of approximately 262,000 kgs. and for l996 of 392,000 kgs.

Prices for BC Pine Mushrooms in Tokyo

The Japan Agricultural News for October 23, l997 reported the following price range for pine mushrooms at Ota Market in Tokyo. This price is given in yen/kg and includes the 5% consumption tax. At the time the exchange rate was 88.52 yen/$Can. (Source: Japan Agricultural News).

Figure 2. Price Range for Pine Mushrooms (yen/kg.)
(source: Japan Agricultural News)

Country of Origin	High	Medium	Low

Canada	7350	4200	3150
US	4200	3675	2625
China	12600	8400	6825
Korea	26250	26250	18900
Japan	65625	34125	26250
(Hiroshima region)			

These price differentials arise, among other factors, because different countries produce different species of pine mushrooms and these have different shapes, colours, smells textures, and other qualities which appeal to the Japanese consumer. Also the price for a country's product is dependent on market availability of species from other source countries. It should be noted that if the price of Canadian pines rose to the level of those from the Republic of Korea, the total pine revenues paid to our exporters would increase by a factor of around six.

If we assume that BC could eventually annually export around 600 tons of matsutake to Japan, with an October 23, l997 exchange value of 88.52 yen per Canadian dollar and price of 8,000 yen per kilogram retail, this crop would presumably be worth around Can. $49 million in Tokyo. Assuming the other food mushroom exports eventually equal this amount, the total BC wild food mushroom exports would be around Can. $l00 million in a good year.

Prices and Pests

In l997, a lower than normal price year for pines, buyers reported that they received approximately US $35/kg. on average for all grades, although at times during the harvest season received up to US $95/kg. for #l's (the best grade).

Part of the price differential between Canadian pines and Japanese or Korean pines is accounted for by the fact that the latter two mushrooms are farmed in cultivated forests, grown in stringent conditions in those countries and controlled for insect infestation. Canadian pine mushrooms are attacked by several species of fly larvae, and this is a major factor in our lower prices.

Station buyers, of course, attempt to determine if the mushroom is wormy by squeezing, smelling and visually examining it, but typically if on the first day one hundred pounds of pines are brought to a station for purchase, roughly one quarter to one third of these are infested, but only ten percent of the infested mushrooms are detected by the buyers. In the second day, the buyer further removes, on average, ten to fifteen percent of the purchased mushrooms as infected, but even so, by the time the mushrooms reach the auctions of Osaka and Tokyo, a further fifteen to twenty percent will eventually prove to be wormy. This situation is generally acute only during August and early September, when it is warm and infestations are accelerated. But such infestation and discarding at various stages continues throughout the harvest season. Since pest infestation is more prevalent in warm climates, the percent of BC sales to Japan which is first imported from warmer US growing areas in Washington and Oregon and sold as a BC product contributes to comparatively high infestation rates of the "Canadian" products and thus to the decade-long stagnation of prices paid for BC products. When a Japanese wholesaler purchases pines from Japan or Korea, he knows they will not be infested since they are grown under pest-controlled conditions. A possible response to these problems is discussed in Part II.

The Japanese Market for Pine Mushrooms

In Japan the mushrooms may go through up to six levels of wholesalers before they are sold to local retailers. After being unloaded from the planes, they are first sold as rapidly as possible at the morning auctions for wholesalers (general public forbidden) in Tokyo and Osaka. A wholesale buyer has five seconds to bid on a 2kg box (five 400 gram containers) as it passes in front of him. He is not allowed to touch them but tries to determine larval presence through sight only. Sold mushrooms are then hauled across the street from the Osaka auction where another layer of wholesalers buy them at fixed prices and so on down the line.

The final (high end) consumer product, a single pine mushroom enclosed in a beautiful small pine wood box with a piece of fern in the background and sealed on the top with transparent plastic, may retail for up to US$150. This will be purchased and taken home to be very thinly sliced and consumed over a week by an entire family.

Pine mushroom production has fallen in Japan since the mid l800's when consumption was around l2,000 metric tonnes annually (Weigand l997). Present consumption is estimated at around 4,000-5,000 tonnes per year. The Japanese prefer the species *T. matsutake* from Japan, (and then Korea), and lower grades are often frozen and used by food manufacturers. The Korean matsutake, which gets considerably higher prices than the Canadian product is so devoid of flavour that it is sometimes injected with pine oil before being imported to Japan. Nevertheless the price differential between Canadian and Korean pines is mainly accounted for by the fact that the preferred Korean and Japanese matsutake look very similar with respect to the long narrow stem and smaller, brownish cap. (Since Japanese consumers accept the Korean pines adulterated with pine oil, they might equally accept Canadian pines whose caps are stained with some organic substance such as soy so that they more resemble Matsutake).

Japan consumes both domestically-produced and imported pines. Between l991-l995, Japan production comprised only between three to sixteen percent of all pines consumed (Weigand l997), and invasion of Japanese stands of red pine (*Pinnus densiflora)* by insect and nematode pathogens has vastly decreased the pine harvest in Japan after l960. Present harvest is about one tenth of that in the early fifties. Even with the rising pine imports, total pine mushrooms on the Japanese market are still considerably less than the Japanese domestic harvest of the l950s.
Since pine mushrooms are obligate mycorrhizal partners with trees, to date no one has been able to culture them artificially to the levels of commercial production.

The Japan Tariff Association has kept records of pine imports to Japan since l976 and included shiitake and truffles since l993. Figure 3 presents value and volume of imports by species group for l993-l995.

Figure 3. Value and Quantity of Imported Fresh and Chilled Mushrooms to Japan, 1993-1995.

value in billions of constant 1990 yen;
Volume in metric tonnes, (in parenthesis)

Species	1993	l994	1995
pine mushrooms (*Tricholoma spp.)*	13309 (l9443)	19262 (3622)	20136 (4993)
Shiitake *(Lentinula edodes)*	9316 (l5586)	10456 (24316)	9608 (26308)
truffles (*Tuber spp.)*	253 (4)	289 (5)	344 (5)
all others	240	266 (655)	340 (572)

source: Japan Trade Association

Weigand (1997) has noted that a “three tier” market has arisen in which Japanese matsutake commands the highest prices; Korean matsutake commands a half to a third of these prices in Japan, and the products of other countries such as Canada command on average a third to a half of the value of the South Korean imports to Japan.

Unfortunately the Japanese and Canadian pine mushrooms are harvested at roughly the same times, but as noted, the Japanese product is really farmed in cultivated forests and controlled for pests. At the experimental forests operated by the Kyoto Forest Experimental Station visited by one of the authors, pine mushroom production by 20 years was around l.9kg/ha and is expected to rise to approximately l00kg/ha by the 35^{h} year. Shaun Freeman (l997) has provided data which allow us to compare the productivity of this (typical) cultivated Japanese tract at 35 years growth with wild gathering in the Nahatlatch Watershed. Freeman found that an area of approximately 5,988 ha in the Watershed produced a minimum of l9,799 kgs. of pine mushrooms in a good year, of which approximately half were harvested. (In Kyoto, almost the entire crop is harvested). These figures would indicate that the wild Nahatlatch harvest yielded approximately l.65 kgs./ha harvested, compared with l00kgs./ha at Kyoto, or one sixtieth of the latter projected harvest. Although the hypothetical Kyoto production is still twenty years in the future, this comparison allows us to see the types of productivity increases possible through cultivation forests in BC dedicated to *T. magnivelare* maximisation.

Market Values for Pine Mushrooms vrs. Timber

Freeman’s data also allows us to perform a crude estimate of the comparative market value of the pine mushrooms versus the value of the timber in one area of the Nahatlatch Watershed. The timber in this area is mainly open stands of H Class 7-8 Douglas Fir which are approximately l40-250 years old, plus Hemlock and Balsam. Excluding non-commercial cottonwood, aspen, birch and maple, Figure 4 presents volume estimates of the main commercial species growing in 27,683 ha. of the Nahatlatch Watershed. These prices in Figure 4 are averaged from six months of prices during l998. The average market price used for pine mushrooms in these calculations was US $20/lb, a three year average.

Figure 4. Nahatlatch Timber Area and Volume/Price Data (Area: 27,683 ha.)

Species	Volume (cu. metre)	Average Price ($CDN/cu. metre)
Fir	3,489,630	$111.00
Spruce	624,690	$67.00
Cedar	855,996	$132.00
Hemlock	2,851,608	$67.00
Balsam	3,076,417	$67.00
Cypress	62,442	$123.00
Pine	706,654	$ 54.00

Source: Timberline Consultants

Freeman's figures for the pine mushroom crop were taken in a good year. If we conservatively assume: (l) on average that annual yearly fruiting of pine mushroom volume on this 5,988 ha parcel of land is half of his value; (2) that all of the logs are harvested and sold after the accepted maturity cycle of l20 years and that all of the mushrooms are harvested annually; 3) that all of the timber in figure 4 is currently mature and evenly distributed over the entire 27,683 ha, then we can do an area conversion and compare the crude market value of timber growing on the smaller parcel over a l20 year maturity cycle with the value of the pine mushrooms. Thus assuming that this land is clearcut now and again after l20 years, and also assuming that prices for timber and pine mushrooms remain stagnant or rise proportionally, the timber will fetch approximately Can. $426 million with two harvests. But if only pine mushrooms are harvested, they will fetch approximately Can. $73 million in constant l998 dollars over the 120 year cycle, or around l7% of the market value of the timber.

This comparison is, of course, based on a wild productivity level of around l.65 kgs./ha harvest. If we assume that Asian agroforestry techniques could be rapidly introduced into this area, then the percentage quickly increases. Assuming, for example that half of the 5,988 ha achieves half of the anticipated 35th year productivity level at Kyoto, that is, 50 kg./ha, then over two timber harvests or l20 years, the value of the pines is roughly twice the value of the timber.

Japanese Price Trends for Pine Mushrooms

Weigand (1997) has projected prices for Pacific Northwest pine mushrooms based on differing assumptions of future per capita income in Japan to the year 2020. Real pine mushrooms prices, he finds, will increase as long as the Japanese economy grows at even modest rates of l.5% annually. This model also assumes that there will not be some major breakthrough in artificially growing pines to the stage of commercialization as there has been with non-mycorrhizal species such as shiitake. Surprisingly then, in spite of the deep current recession of the Japanese economy, prices for pine mushrooms are strong, with #ls and #2s fetching Can. $l00/kg and #4's and #5's in the range of Can. $28-38 in the Nass Valley in October l998 (S. Mills personal communication). The hot weather from El Nino dried out much of the mushrooms patches in the south of BC during the l998 harvest, and the Nass was one of the few places where they were prolific.

In the foreseeable future then, it would seem that Japanese consumers can absorb all the pine mushrooms which BC can export; therefore, the limits to export become the limits of sustainable harvesting plus cultivation. The Canadian pine mushroom industry is underdeveloped compared to what it could be, and these general market prognoses would point toward more intensive forest-based cultivation of pine mushroom areas to increase the export volume as has been done in South Korea, targeting forest types best suited to enhanced commercial yields, implementing agroforestry projects in appropriate productive stands and more extensive marketing and market research to aid the private sector effort in Japan and Asia. These matters are discussed in Part II.

Intensive expansion of *T. magnivelare* in BC through a variety of means provides an opportunity to diversify forest production and South Korean practices provide an economically successful model. In spite of a tiny forest base, intensive in-situ cultivation in that country has resulted in a situation where pines comprise 3% of all Korea's forest products revenues (Gamiet l998).

BC Industry Structure

We were able to identify sixteen active companies exporting wild food mushrooms (of several species) from BC. Over 90% of all exports from Vancouver to Japan of pines are controlled by seven companies, (six of which are Canadian-owned). In a good fruiting year for pines, these seven companies have collective before-tax revenues from pines and other mushrooms of approximately Can. $40-$45 million but in a bad year this figure can fall to around Can. $25 million. Individual mushroom revenues of these seven companies ranged in a good year from Can. $22 million to under Can. $l million. We have identified only three BC companies involved in the export of nutraceutical and medicinal mushrooms, however there are dozens in Oregon and Washington states.

Although over the past decade, the pine harvest has approximately doubled, the average price paid to exporters has remained the same ---around US$l9.00-$20.00/lb. In l997 there was a brief price war for pine mushrooms in the Nass valley. Some companies which had been inactive for several years re-entered the pine market and when this happened, several large, established companies raised the field price paid to harvesters to the range of Can.$35.00-$50.00/lb, driving the new entrants from the field. (When this occurred, some companies lost in excess of Can. $50,000 in a two week period). At the same time the wholesale price for pines in Tokyo and Osaka was around yen 5,300 –an anomalous situation in which the field price paid to pickers was almost twice the landed price in Tokyo. Canadian pine exports have grown at roughly l0% annually since l993, and the combined Oregon and Washington state wild food mushroom industry has grown at an average annual rate of around 12% since l987. (K.Blatner, personal communication).

Pine Mushroom Research in BC

Comparatively little is known about the biology or ecology of our species of pine mushroom, *T. magnivelare*. Most of what we know is based on inferences from Japanese research on a sister species, *T. matsutake*. In spite of the fact that *T. magnivelare* is our most valuable wild food mushroom with apparently guaranteed markets, little research has been performed in BC. S. Berch (l996) has conducted a year of field work with the Nisga'a Tribal Council in the Nass Valley developing procedures to assess pine productivity and ecology, and F. Fogarty through Master's work (l999) has investigated the saprophytic and mycorrhizal capacity of pine mushrooms and has also correlated timber harvest methods with pine production (l998).

Fogarty's thesis deals with the culture of pine mushroom mycelium, examination of its enzymatic capabilities, the use of resulting colonies for *in vitro* ectomycorrhizal trials with conifer seedlings, the analysis of its below-ground ectomycorrhizal form (i.e. root-tip morphology from soil core samples collected directly beneath sporocarps) and lastly the analysis of colonies (shiros) and mushroom production and distribution at different elevations in the field. More recently Fogarty has been examining the isolation, growth, maintenance and expansion of pine mushroom mycelium. Numerous tissue cultures have been isolated from throughout BC and are being grown on both solid and liquid media for extraction and analysis of pharmacologically active compounds as well as for use as inoculum *in vitro* (ectomycorrhizal synthesis with aseptically grown seedlings) and *in vivo* inoculation trials (field inoculation of cultivation forests). Isolates have been confirmed as *T. magnivelare* using DNA analysis techniques.

The mycelial biomass of these isolates is presently being expanded on both solid and liquid media for use as inoculum for pine mushroom enhancement trials in the Sunshine Coast Forest, and Fogarty is currently examining a number of field inoculation methods in both first and second growth forests including:

1) Spores isolated from pine mushrooms and directly applied to specific candidate trees in Douglas fir/ western hemlock stands.
2) Sporocarps (whole mushrooms) ground up and incorporated as a slurry to soil.
3) Vegetative mycelium-tissue cultures isolated from young #1 mushrooms (buttons or primordia) applied both in the field and laboratory inoculation trials.
4) Spawn-increased mycelial biomass (both on solid and liquid media) applied as above.
5) Seedling transplants - select species of tree seedlings planted into the colony or shiro in the field and resulting colonized seedlings transplanted to new sites in both first and second growth stands.
6) Shiro transplants- prior to timber harvest pine mushroom colonies are located, and removed (literally dug up) and relocated to adjacent stands (F. Fogarty personal communication).

The implications of such research are far reaching and may help to alleviate some of the ecological stresses imposed on pine mushroom producing sites caused by timber harvesting activities as well as site disturbance (e.g. soil compaction, raking, wildlife disruption, littering and over-picking).
In addition, S. Freeman (l997) has conducted productivity and ecological research on pines in the Nahatlatch Valley, and S. Gamiet (l998) has conducted an overview of pine mushrooms in the Skeena-Bulkley region.

Other Wild Food Mushrooms (Chanterelles, Morels, and Boletes):

Chanterelles

In a good year, approximately 750,000 kgs. of chanterelles are harvested in BC, although in a bad year, this harvest can fall to a quarter of this number. (Experienced pickers believe that the main factors effecting fruiting are the amount and timing of air and ground temperature and moisture).
The main regions where chanterelles are harvested (in decreasing comparative quantities) are Vancouver Island, Haida Gwaii, Powell River, the Sunshine Coast and the areas around Chilliwack, Hope and Pemberton. Chanterelles (and all the so-called European mushrooms) grow in many places throughout the province but are often not picked. Experienced pickers, for example, estimate that dozens, if not hundreds, of thousands of kilograms of chanterelles grow in the Nass valley region but are left to rot. Generally the European mushrooms are not harvested in regions where pines are present due to the considerably higher market value of the latter fungi. Compared to pine prices, the low prices paid for chanterelles restricts the range which pickers will drive to hunting grounds and also determines the locations of buying stations.

In the following discussion prices are given in the unit and currency actually paid to pickers and exporters. For example pickers are paid in Canadian dollars per pound picked.

Pickers receive on average between Can. $2.00-$4.00/lb for chanterelles and an average selling price of Canadian exporters is in the range of US$l0.00-$l5.00/kg fresh and landed in the US or Europe. In l996, for example, 253,000 kgs. of fresh chanterelles were imported from Canada to France at an average landed price of US $10/kg. (In total, from all source countries, France imported l,477 tonnes of fresh chanterelles in l996 and l,l84 tonnes of dried wild mushrooms of all types, of which two tonnes originated from Canada). (Source: Yannick Dheilly, Commercial Officer, Canadian Embassy, Paris).

Boletes

In a good fruiting year, approximately l00,000 kgs. of fresh boletes are harvested in BC, mainly from Haida Gwaii and the Prince George area. In a bad year there may be virtually no harvest at all. These mushrooms are so weather dependent that it is not possible to rank order their source areas. Again boletes grow in many places where they are not harvested.

Pickers on average are paid Can. $2.50/lb for boletes (there are four grades), and exporters receive US $8-12.00/lb landed and fresh, around US$75.00/kg. dried and landed, and around US$5.00-6.00/kg frozen. Approximately 90% of all harvested boletes are exported dried or frozen and only around l0% of the harvest is exported fresh. Boletes are one of the first wild food mushrooms to be attacked by pests, (they can change grades in three hours), and there is currently a world shortage of king boletes.

Morels

In a good year, approximately 225,000 kgs. of morels are harvested in BC and the Yukon but in a bad year this figure may fall to the range of l0,000-20,000 kgs. (It is generally BC pickers who perform the Yukon harvest). Seventy five to eighty percent of all morels exported from BC come from the Yukon (because BC does such a good job in suppressing forest fires), with the remainder arising from the Pemberton area, the southern Okanagan and the Smithers area (in decreasing order of importance). There are two grades of morels and pickers receive, on average, Can. $3.00/lb for fresh morels, with exporters receiving US $l8.00-$22.00/lb fresh and landed, or in the range of US $l00.00-$125.00/kg dried and landed in the US or Europe. Both boletes and morels are exported fresh only about two weeks of the entire growing season because they are rapidly attacked by pests.

Additional Food Mushrooms

In addition to the so-called "big four" wild food mushrooms from BC (pines, boletes, morels and chanterelles), there are some small emerging sales of other food mushrooms such as lobster, secondary boletes, cauliflower, sweet tooth, hedgehog, and other mushrooms. These other food mushrooms together presently account for a harvest of around 50,000 kgs./year throughout the province and sellers receive around Can. $50.00/kg. dried and landed on average for these species. These mushrooms are generally sold fresh only in the US and in very small volumes. The sale of dried Lobster mushrooms is just beginning to Europe, and several companies expect to receive in the range of US$40.00-$50.00/kg. for dried lobster mushrooms. Another wild food mushroom species generally ignored in BC is the truffle. (The North American Truffling Society has estimated that a single older forest acre replete with mushrooms can annually produce up to US $240,000 worth of truffles). Although we were not able to separately determine BC truffle exports or consumption, Pilz and Molina (1996) report that about 32,000 kgs. of Oregon white truffle (*Tuber gibbosum*) were harvested in Oregon and Washington in l992, with prices averaging US$32/lb. They also interestingly note that some early Oregon marketing attempts failed because they presented immature, odourless truffles to consumers, located by random raking rather than the ripe, aromatic fruit found by trained animals.

The above estimates for "good" and "bad" year harvest quantities of the European mushrooms are based on two sources – averages of buyer estimates at field stations for their regions taken in the fall of l997 and import data from the consuming countries. The latter information sources proved scant and generally are given in the category of "wild mushrooms" with no species specifications. To give just one example, Switzerland gives import statistics in terms of "wild mushrooms" - classification No. HS 0709.5100. In l996, Switzerland imported 2,l64 tonnes valued at 20.4 million SFr and in l995 2,022 tonnes for l9.3 million SFr. Out of a total of 2l supplier countries in l996, Canada ranked 7th in terms of volume, supplying 83 tonnes at l,446 million SFr. (At that time the Canadian dollar and the Swiss Franc were approximately on par).(Source: Michel Tetu, Central Europe Division, Dept. of International Trade and External Affairs, Canada).

In order of importance, the consuming countries for BC chanterelles, boletes and morels collectively

are France, Germany, Italy, Switzerland and the Netherlands. France serves as the major redistribution centre for Europe.
Collectively, in a good year, over l million kgs. of chanterelles, boletes, and morels are exported from BC (if we include the Yukon component of morels). There are approximately 6,000 pickers in BC during harvest time who receive an average daily wage of Can. $50.00-$l50.00. In most regions of the province, around two thirds of all pickers are locals and one third professional, migratory pickers. In the fall of l997, Asian pickers were a noticeable presence for the first time in the Nass valley (around 3-4% of the picker force of 2,600).

We have attempted to identify "best bet" BC food mushrooms which could be harvested and exported to the US, Europe and Asia. These species are represented in bold in Figure 5. Criteria of identification involved volume available in BC, consumer preferences and trends, proven markets in regions of the US, etc. (Figures 5 and 7 were compiled with the guidance of F. Fogarty, S. Redhead and S. Gamiet).

Figure 5. Edible BC Wild Food Mushrooms
(not exhaustive)
(bolded represent "best economic bets")

Genus/Species	Common Name
Armillaria ostoyae and allies	**Honey Mushroom**
Auricularia auricula	Tree Ear
Aleuria aurantia	Orange Peel
Boletopsis leucomelaena	Kurotake
Boletus edulis	**King Bolete**
Boletus mirabilis	**Velvet Top**
Boletus smithii	Smith's Bolete
Boletus zelleri	Zeller's Bolete
Cantharellus formosus	**Pacific Golden**
Cantharellus infundibuliformis	**Funnel Chanterelle**
Cantharellus subalbidus	**White Chanterelle**
Cantharellus cibarius var. roseocanus	**Rainbow Chanterelle**
Clavulina cristata	**Crested Coral**
Dacrymyces palmatus	Orange Jelly
Gomphidius oregonensis	Oregon Gomphidius
Gomphidius subroseus	Rosy Gomphidius
Gomphus clavatus	Pig's Ear Gomphus
Hericium abietis	**Connifer Coral Hericium**
Hydnum repandum	**Hedgehog**
Hygrophorus bakerensis	Mount Baker Waxy Cap
Hypholoma capnoides	Smoky Grilled Wood Lover

Genus/Species	Common Name
Hypomyces lactifluorum	**Lobster Mushroom**
Laccaria laccata	**Common Laccaria**
Lactarius deliciosus	**Delicious Milky Cap**
Lactarius rubrilacteus	Red Juicy MilkyCap
Laetiporus sulphureus	**Sulphur Shelf**
Lycoperdon periatum	Stuffed Puffball
Lycoperdon pyriforme	Pear Shaped Puffball
Lyophyllum decastes	Fried Chicken Mushroom
Morchella esculenta	**Yellow Morel**
Morchella elata	**Black Morel**
Pleurocybella porrigens	Angel Wing
Pleurotus ostreatus	**Oyster Mushroom**
Pluteus cervinus	Deer Mushroom
Polyozellus multiplex	Blue Chanterelle
Pseudohydnum gelatinosum	White Jelly
Rozites caperata	Gypsy Mushroom
Russula xerampelina	**Shrimp Mushroom**
Sparassis crispa	**Caulliflower Mushroom**
Suillus brevipes	Slippery Jack
Suillus caerulescens	Blue-Staining Slippery Jack
Suillus cavipes	Hollow Stemmed Larch Bolete
Suillus granulatus	Dotted Stalked Slippery Jack
Suillus lakei	**Lake's Bolete**
Suillus lufeus	**Slippery Jack**
Suillus subolivaceus	Slippery Jill
Suillus tomentosus	Woolly Capped Bolete
Tremella lutescens	Witches Butter
Tricholoma caligatum	Fragrant Pine
Tricholoma flavovirens	Man-On-Horseback
Tricholoma magnivelare	**Pine Mushroom**
Tricholoma portentosum	Streaked Tricholoma
Tuber gibbosum	**Oregon White Truffle**

Price Trends for Wild Food Mushrooms in the US

Keith Blatner and S. Alexander (in preparation) have examined prices for seven commonly harvested mushroom species in the US Pacific Northwest. These prices are very volatile as reflected in the annual variations of Figure 6. In general these prices are lower than prices paid to BC pickers for BC products.

Figure 6. Mean Prices in Current US Dollars for Selected Wild Edible Mushroom Species Harvested in Oregon, Washington and Idaho, per Pound

Name	1992	1994	1995	1996
Boletes	$4.53	$6.40	$5.51	$6.63
Chanterelles	$3.09	$4.00	$3.02	$3.06
Hedgehog			$3.29	$4.86
Morels	$4.14	$5.86	$4.57	$5.60
Matsutake	$8.37	$17.00	$18.69	$12.26
Truffles	$31.62		$24.80	

Source: K. Blatner and S. Alexander

As of January l998 there are no restrictions on the international trade in wild mushrooms, but given the fact that more picker permits and restrictions will probably be instigated in the US to control for the amounts of mushroom harvesting and given the environmental catastrophes in the Asian forests such as the on-going burning during l998 of the Indonesian forests, prices of both food and nutraceutical mushrooms may rise drastically over the next five years.

IV. Medicinal and Nutraceutical Mushrooms

The medicinal and nutraceutical mushrooms, extracts, and products built on these have greater economic potential for BC than the wild food mushroom crop.

North American medical research on mushrooms is scant, and BC's first nations peoples do not have an extensive history of using mushrooms for medicinal purposes (Nancy Turner personal communication). But medical research in Asia (mainly in Japan and China) and in the Russian Far East includes diverse research programs investigating the therapeutic effects of mushrooms, their mycelia and extracts. Mushrooms have been traditionally ignored by medical and nutritional researchers in the west, and many western cultures are "fungophobic" for reasons too complex to describe here. Also, western medicine has traditionally sought "magic bullets" effective against specific pathologies and whose underlying physiological/chemical mechanisms could be elucidated. Until recently substances with alleged immune-boosting properties and hence potentially effective against a wide range of divergent pathologies were simply dismissed as nonsense. All of this is changing.

Many anti-tumour components have been developed from mushrooms in Japan and commercialized into products (Mizuno l995). In addition to general immune-boosting properties, many mushroom and mycelium derivatives have also been found effective, to varying degrees as anti-viral, anti-bacterial and anti-parasitic agents and in alleviating certain side effects of acquired immune deficiency syndrome (Mizuno *et al.* 1995).

One of the main results which has emerged from literally hundreds of laboratory and human clinical studies during the last thirty years is that ingredients of a variety of fungi can both inhibit tumour growth and improve the functioning of the immune system. Specifically compounds named polysaccharides – large branched, chain-like molecules constructed of many small units of sugar molecules – have been intensely scrutinized and found to have both anti-tumour and immune stimulating properties. Such polysaccharides are found in both fungi and lichens which are native to BC. The immune-stimulating polysaccharides found in many BC fungi species are also found in some higher plants, such as *Echinacea,* one of the fifteen top herbal remedies which currently collectively account for a world herbal market of US $ll billion (Chatfield Dean & Co. undated).

Polysaccharides and other ingredients in fungi such as terpenes and steroids have also been found to have antibiotic and antiviral properties, to reduce the levels of lipids in blood and to lower blood pressure. Ingredients in medicinal mushrooms have clinically been found to stimulate the production of white blood cells, antibodies and interferon (an anti-viral protein) and to inhibit the synthesis of prostaglandins (locally acting hormones which regulate blood vessel size). Other fungal extracts such as those from *Lentinula edodes* have been found to inhibit HIV infection of *in vitro* cultured human T cells in clinical trials (Iizuka *et al.* l990, l990a) and in a variety of cases have been found to extend the survival rate of patients with illnesses ranging from Hodgkin's disease to lymphosarcoma, and pancreatic cancer (Hobbs l995). Although polysaccharides are a broad and common type of molecule present in the majority of the food we eat, specific polysaccharides such as PSK, which are present in a wide variety of BC fungi, are thought to have the medicinal properties described above.

(Many of the fungal extracts which are classified as drugs in Canada are classified as food supplements in Japan. This fact is taken up in the policy sections).

Nutraceuticals – Immune Stimulators and "Adaptogens"

Nutraceuticals can act either as an immune stimulant or as an "adaptogen". It is currently thought that polysaccharides from shiitake (Ladanyi *et al.* 1993), *Cordyceps spp.* (Zhang *et al.* 1987, l993) and from *Trametes versicolor* (Yang *et al.* 1993) plus a wide variety of other fungi indigenous to BC all increase the level of macrophage activity and thus fortify the immune system's combating of viruses and bacteria.

"Adaptogens" on the other hand, are defined as substances which aid the body to adapt to environmental and psychological stress. Farnsworth (l985) has shown that the pharmacological effects of the so-called adaptogenic herbs may be quite complex (for example supporting adrenal functions). Adaptogens are thought to enhance immunity indirectly through "balancing" the endocrine system. Some laboratory tests (Locke and Hornig-Rohan l983) have found that adaptogenic substances aid cells in the more efficient use of oxygen and increase cellular respiration efficiency.

At the same time mainstream medical research has been investigating for more than ten years the ways in which the immune, hormonal and nervous systems are interconnected and affect one another. Hobbs (l995) cites the well-known example in which excess cortisol hormone released from kidneys in response to stress depresses the immune system.

Certain adaptogenic mushrooms (together with many other health herbs such as *Panax ginseng)* also contain large amounts of the element germanium (Reynolds l993, see also Hung-Cheh and Mieng-Hua l986) which both increases the absorption and use of oxygen in body tissue and protects from damage arising from free radicals which are generated by such extra oxygen.

For the purpose of this study a nutraceutical is defined as a substance which has either prophylactic, immune stimulating or adaptogenic effects when consumed or tissue injected. (Many polysaccharides are not absorbed when eaten but pass through the body).

BC is one of the world's most economically-valuable, environmentally-pristine sources of nutraceutical and medicinal mushrooms, and among these are both relatives of species used for centuries throughout Asia for treatment of specific illnesses and immune stimulation, and other species being consumed as "nutraceuticals" by both Asians and increasingly an aging boomer population in the US.

A nutraceutical then, is something one eats to stay healthy or to get healthier, to enhance the immune system even when one is not sick. If this is a slice of pine mushroom costing $25 in a local specialty restaurant, so much the better. Nutraceuticals are sometimes also called "functional foods". A wide variety of native BC mushrooms are thought to be immune stimulators. According to traditional Chinese medical theory, the nutraceutical mushrooms are part of an herbal category called Fu-Zheng, which increases disease resistance and "normalizes" bodily functions.

*Ganoderma lucidum (*also called Reishi in Japan and Lingzhi in China*)* and related species native to BC containing active polysaccharides, triterpenes and other substances are utilized throughout Asia in both traditional medicine and mainstream medical research. Japanese scientists have identified in excess of one hundred ganoderic acids (triterpenes) in Reishi and research in Japan, Russia and China have found circulatory system and allergy benefits. A polysaccharide called PSK from *Trametes versicolor*, a relative of *G. lucidum*, is used in Japan to suppress the spread of tumour cells and sells dry in Osaka for US $l,500 - $2,000/kg. However selling raw or dried source material is only one way to derive revenues.

Similarly *Fomitopsis pinicola,* another native BC species *and F. officinalis* are thought to possess both immune-enhancing and specific medicinal effects. *F. pinicola* was used extensively by the Cree of eastern Canada for fevers, chronic diarrhoea and dysentery, and for chills in consumptive patients. Polysaccharides of this species have moderate tumour inhibiting properties against sarcoma l80 (Ito *et al.* 1973) and have been used for centuries in traditional Asian medicine to reduce digestive tract inflammation and as a cancer preventative.

Another common BC species, *Schizophyllum commune,* contains an extract called SPG which is used in contemporary mainstream medicine of Japan for a variety of purposes. A polysaccharide from this species, SPG, has shown antitumor activity against both solid and ascites forms of sarcoma l80 and against solid forms of saracoma 37, Yoshida sarcoma and lung carcinoma (Yamamoto *et al.* 1981, Komatsu l969, Tabata *et al.* 198l). Oka *et al.* (l985) found that *Schizophyllan* (SPG) increases cellular immunity through restoring T-cell activity to normal levels in mice with tumours, and this substance has long been known to have protective effects against *Pseudomonas aeruginosa, Staphylococcus aureus, Esherichia coli, and Klebsiella pneumoniae* infections in mice (see Komatsu *et al.* 1973). In human clinical studies SPG administered to patients with inoperable gastric cancer combined with chemotherapy significantly prolonged life over those who received chemotherapy alone (Furue l985), and similar results were found with cervical cancer patients receiving radiation therapy with and without SPG (Okamura *et al.* 1989, Yoneda *et al.* 1991, Yang and Jong l989). A study by Kakumu *et al.* (l99l) also suggests that SPG benefits chronic hepatitis B patients, since SPG enhances immune response to the hepatitis virus through the production of interferon-g.

Neither *Schizophyllum* nor many of the medicinal mushrooms discussed here are available in Europe or North America commercially in bulk. In Japan *Schizophyllum* is consistently prescribed in cancer therapy together with other treatments.

Trametes versicolor (Yunzhi or Kawaratake) another common BC fungal species has been the subject of much clinical research in Japan and PSK extracted from this fungus accounts for around 16% of Japan's national expenditures on anti-cancer agents (J.Fukushima, personal communication). *T. versicolor* ingredients are also thought to enhance T-cell proliferation and are taken in Asian countries as a nutraceutical. In Japan a nutritional supplement containing *T. versicolor* is generally used as a health food, and testing in Japan has shown that it has cholesterol-lowering properties (Mitomo *et al.* 1980). Dried PSK retails for around US $2,000/kg. in Tokyo.

Pharmacological effects of *T. versicolor* ingredients such as PSK, include the following examples cited by Hobbs (l995); inhibition of sarcoma l80 (Yan l985); restoration of serum lysozyme content and normalization of spleen index (Cao et. al l986); effective against lethal cytomegalovirus infection (Ebihara and Minamishima l984); *in vitro* cytotoxicity against hepatoma cells (Valisolalao *et al.* l983); stimulation of phagocytotic activity of macrophages and improving functioning of reticuloendothelial system (Zhu l987); antitumor activity in animals with adenosarcoma, fibrosarcoma, mastocytoma, plasmacytoma, melanoma, sarcoma and mammary, colon and lung cancer (Tsukagoshi *et al.* 1984); prevention of metastasis (Ebina *et al.* l987b); antiviral activity through stimulating interferon production (Ebina *et al.* 1987a); at the same time a glycoprotein from the mycelia of *Trametes* species has shown activity in both animal and *in vitro* testing against diabetes, thrombosis, rheumatism, hypertension and several other forms of cancer.

In human clinical studies of the effects of ingested or intravenously administered PSK, there is now a literature simply too vast to be included in a study of this nature. To give a single example in an early study done by the Department of Gynecology at the National Cancer Center Hospital in Tokyo (Kasamatsu l982) the effects on survival rates of PSK were investigated with patients with cervical cancer. PSK was orally administered at three to six grams per day in conjunction with radiation therapy.

At the end of the radiation treatments, the population of patients with no observed tumour cells was 36% with PSK and ll% without it. Five year survival rates were 64% with PSK and 41% without.

If we include the microfungi, less than l0% of all fungi in BC has even been identified much less chemically analyzed for alleged nutraceutical ingredients such as polysaccharides, terpenes and peptidomannans or tested as specific anti-virals, anti-bacterials, etc.

Ganoderma applanatum, a native BC species found in profusion has been found to increase the proliferation of spleen cells, possesses anti-biotic properties and in Sichuan, China, is used to treat TB and oesophageal cancer. RNA from *G. applanatum* has been found to cause the production of an interferon-like substance in the spleen of mice, and nucleic acids which were isolated from this species provide protection against tick-borne encephalitis virus in mice (Kandefer-Szerszen *et al.* 1979). Gao and Yang (1991) found that polysaccharides from *G. applanatum* both increase the proliferation of spleen cells *in vitro* and have anti-tumour activity against sarcoma l80 in mice.

Ganoderma tsugae, a rare BC species (but prevalent in the east), is one of the most cultivated Ganoderma species in Taiwan and China along with *G. lucidum* and is consumed in several Asian countries as a nutraceutical. Three of the several triterpenoids found in Reishi –lucidone A, ganoderic acid B and ganoderic acid C have been identified in *G. tsugae*, and Su *et al.* (l993) have found that ganoderic acid B from *G. tsugae* provides effective protection from carbon tetrachloride-induced liver toxicity. Wang *et al.* (l993), Won *et al.* (l992) and others have also found that the fruiting body contains several polysaccharides with strong antitumour activity against sarcoma l80 in mice.

To give another example, mycelia extracts from *Cordyceps ophioglossoides* contain polysaccharides with alleged immune enhancing properties and it is used in the traditional medicines of Vietnam, Taiwan, and China to treat a variety of ailments, including upper respiratory infections, chronic bronchitis, pulmonary emphysema and tuberculosis. Two polysaccharides from this species, CON and SNC, have been reported to stimulate the immune system (Ohmori l988ab, l989ab), and CON has a direct cytocidal effect on tumours in the cases of MM46 carcinoma, Ehrlich carcinoma and P388 leukaemia (Ohmori l989). Ohmori (l989a) also reports that single dosages of 0.5 mg/kg inhibited tumour growth in mice with sarcoma l80 by 98.7%. SNC is also active against a wide range of tumours. *C. ophioglossoides* extracts also apparently have strong anti-fungal and immune stimulating effects and apparently activate peritoneal macrophages (Zhang *et al.* l985). Another polysaccharide extracted from this species inhibits the development of sarcoma 180 tumours in mice (Yamada *et al.* 1984). In China, *Cordyceps* species are regularly consumed as a nutraceutical lung and kidney tonic, for impotence and anaemia.

Auricularia auricula, still another indigenous BC mushroom, is used throughout Asia as a nutraceutical in soups and medicinally in China to reduce the build-up of certain types of blood cholesterol. Xia *et al.* (l987) have found that polysaccharides from this species stimulate RNA and DNA synthesis by human lymphocytes *in vitro* (hence its use as an immune tonic), and polysaccharides from the species have shown these effects on mice: antimutagenic (Zhou *et al.* (l989); anticoagulant (Sheng and Chen l989); lowering of cholesterol, lipid and triglyceride levels (Sheng and Chen l987); antidiabetic and

cytoprotective effects on pancreatic mice cells (Xue *et al.* 1989); antiradical, antileukocytopenic, immunostimulatory and anti-inflammatory (Xia and Chen l989), and antitumor activity on sarcoma l80 in mice (Misaki *et al.* 198l).
To conclude this discussion with a final example, *Grifola umbellata*, (also referred to as *Polyporus)* ,another indigenous Canadian species, called Zhuling in China, contains several polyporusterones which have been found to be cytotoxic on leukemia l2l0 cells *in vitro* (Ohsawa *et al.* 1992), and other extracts from this species have inhibited DNA synthesis in sarcoma l80 with mice (Chang and But l987). Polysaccharides from this species have also been found to offer protection against ionizing radiation (Hu and But l987).

There are literally hundreds of pharmacological and human clinical studies of the effects of *e*xtracts from *Grifola* and other fungal species on a gamut of pathologies. For a comprehensive summary of the chemistry, pharmacology, human clinical studies, contraindications, toxicity and uses in traditional medicine of the nutraceutical and medicinal mushrooms, the reader is referred to Hobbs (l995), Bo and Yun-sun (l980) and Ying (l987).

Finally, phytoestrogens, which are produced by many BC fungal species, are becoming an herbal market category in themselves and are examined in the sections on medicinal botanicals.

Figure 7 contains our "first cut" at identifying the most economically-valuable indigenous medicinal and nutraceutical mushroom species which BC should concentrate on. The more value one can add to the product, the greater the revenues. If one sells dried mycelial extracts, the rewards may be greater than selling the fresh product. If one grows and sells a mycelia extract on an organic substrate, one will receive higher prices from the nutraceutical consumer products industry than if the product is not organic. If one sells a nutraceutical or medicine through a joint venture arrangement with a large distributor, the financial rewards are potentially greater than those for mycelial extracts.

Figure 7. Potentially Nutraceutical and Medicinal BC Wild Mushroom Species
(not exhaustive)

Genus/Species	Common Name
Amanita muscaria	Fly Agaric
Armillaria mellea	Honey Mushroom
Auricularia auricula	Wood Ear
Boletopsis leucomelaena	Kurotake
Boletus edulis	King Bolete
Boletus mirabilis	Velvet Top
Boletus zelleri	Zeller's Bolete
Cantharellus spp.	Chanterelle
Cordyceps spp.	Insect Fungi
Fomes fomentarius	Tinder Polypore

Genus/Species	Common Name
Fomitopsis officinalis	Quinine Conk
Fomitopsis pinicola	Red Belt
Ganoderma applanatum	Artist's Conk
Ganoderma oregonese	Varnish Shelf
Ganoderma tsugae	Hemlock Varnish Shelf
Gloeophyllum separium	Gilled Polypore
Grifola frondosa	Maitake
Hericium abietus	Coral Hydnum
Inonotus obliquus	Chaga
Laetiporus sulphureus	Sulfur Shelf
Lenzites betulina	Gilled Polypore
Morchella esculenta	Morel
Phellinus igniarius	Flecked-Flesh Polypore
Pleurotus ostreatus	Oyster Mushroom
Polyporus spp.	Polypores
Schizophyllum commune	Split Gill
Trametes versicolor	Turkey Tail
Tremella spp.	Witches Butter
Tricholoma magnivelare	Pine Mushroom

Prices for Nutraceutical and Medicinal Mushrooms, Mycelium and Extracts

Figure 8 gives some typical March l, l998 prices from BC and US firms for dried nutraceutical and medicinal mushrooms, mushroom extracts, and mycelia extracts. Different chemicals may reside in mushrooms caps and mycelia, and it is now common practice to use mycelium as an organic, continuous source of polysaccharides. Thus PSK is generally derived from *Trametes versicolor* mycelium.

There are now almost pharmaceutical-grade requirements for nutraceutical and herbal fungal extracts and both product quality and guaranteed potency (standardization of ingredients) are very important. One BC industry leader which exports all over the world, North American Reishi in Gibsons, BC, is the company that first introduced standardized mushroom extracts, developing testing protocols for the gamut of constituents of their products to international standards.

North American Reishi's product groups include: whole cultivated mushrooms, dried mycelium and extracts from select genetic stock and grown on standardized organic substrates. These are selected for maximum triterpene production. Through the use of HPLC, this company has identified Reishi cultivars with very high naturally occurring levels of triterpenes and then achieved organic certification for their products in l997.

Figure 8. Typical March l998 Prices of BC and US Firms for Selected Dried Medicinal and Nutraceutical Mushrooms and Mycelia Extracts

Mushroom or Extract	Qty.	US$ (retail)	US$ (wholesale)
Ganoderma lucidum (Reishi)	1 lb.	$102.00	$22.25
Cordyceps sinense - fruit body and caterpillar (Dong Chong Xia Cao)	1 oz.	$89.00	
Auricularia polytricha	1 lb.	$16.00	
Grifola frondosa (Maitake)	1 lb. 1 oz.	$129.95 $14.95	$25.00
Grifola frondosa water extract, fine powder, 4:l concentration	1 lb.		$120.50
Coriolis Mushroom alcohol extract	1 kg.		$102.25

This price listing requires qualifications. The retail prices are from Fungi Perfecti and Garuda, two US companies, while the wholesale prices are those of North American Reishi and more realistically represent the current market. At least one Reishi farm in BC, motivated by Fungi Perfecti price listings available on the Internet, grew thousands of pounds of Reishi with no real market research and went bankrupt.

Secondly, Jeff Chilton, president of North American Reishi, reports that peak prices have been reached for the time and prices are coming down. The main reason for this is that it is hard to compete at the baseline with the Chinese, who can grow mushrooms cheaper, pick them cheaper and are predatory in their sales strategies. Several large Chinese herb suppliers in the US and China sell dried mushrooms and mushroom extracts for much less than the above prices. North American Reishi is able to compete in the face of these predatory practices because of their superior product quality – highly accurate standardisations of ingredients and organically grown. A stumbling block in BC is the labour costs involved in cultivating mushrooms. Unless the product is a very high value, "semi-precious" item such as matsutake, the labour component often renders the product uncompetitive.

Some producers are making powdered ingredients from nutraceutical mushrooms and their mycelia for use in capsules, health drinks, cosmetics and tablets. In Oregon and Washington, where the nutraceutical and medicinal fungi industry is much more developed (we were able to identify l8 firms in Oregon alone), raw material suppliers have diversified from mushroom and mycelial bulk into a diversity of final consumer products, such as capsules of *Grifola frondosa* which are sold over the Internet.

Production Technology

Determining, and standardizing, the level of ingredients in nutraceutical or medicinal mushrooms, for example terpenes in *Ganoderma lucidum*, requires a sophisticated ability in analytic chemistry and HPLC (high performance liquid chromatography). Several laboratories at UBC can do this, and in the BC private sector there are six facilities which can perform these tasks – JR Laboratories (the privatized BC government labs), Canadian Phytopharmaceuticals, Elemental Analysis, Phytogen Life Sciences, Okanagan Ginseng Lab. Ltd, and the UCC Ginseng Testing Centre in Kamloops. The production technology for natural products testing is described in the sections on "Medicines from Plants". Almost all of the above companies are three years old or younger, and before their existence, several BC growers of medicinal botanicals who tried to move down line and make products were burned when contract manufacturers who claimed they could produce standardized products could not deliver the goods.

Markets for BC Medicinal and Nutraceutical Mushrooms

The annual world market for nutraceutical and medicinal mushrooms is estimated at approximately US $l.3 billion –US $900 million in Japan plus the rest of Asia, US $250 million for Europe and US $l50 million for North America.

1. The US nutraceutical market—strictly speaking, nutraceuticals in the US are products sold as nutritional supplements under the Dietary Supplement Health and Education Act, which may have therapeutic activities. Currently fifteen popular botanically-derived herbals such as Saw Palmetto (benign prostatic hyperplasia) and St. John's Wort (depression) capture over 75% of the world's estimated US $l1 billion herbal medicine /nutraceutical market.(Chatfield Dean & Co. undated). Gunner (l998) has estimated the US nutraceutical market as $2.7 billion in l997, with the Canadian market as $270 million, although other estimates put this figure currently at $4 billion annually for the US with equivalent figures for Europe and Japan. For example The New York Times of July 23, l998 has estimated that nutraceutical sales (that is, sales of vitamins and minerals plus herbal supplements) in the US increased by l8% in l997 to US $3.6 billion and by 75% in all since the l994 regulatory changes were adopted in the US. It is predicted that sales in the year 2000 will exceed US $7 billion. Another source (Schroder Securities Limited undated) has put the annual global nutraceutical market at US $7.5 billion and predicts that it will be in excess of US $l3 billion by the year 2000. (Several countries and regions are moving to support their nascent nutraceutical industries. For example the government of Saskatchewan announced in October l998 the provision of $l million to help launch the Saskatchewan Nutraceutical Network which will help market and promote nutraceutical, functional food, and "dermaceutical" products from that province).

With the revised guidelines of the l994 Dietary Supplement Health and Education Act, manufacturers of herbal supplements, which hitherto had been forbidden to make any health claims about their products, were allowed to advertise potential health benefits, without conclusively proving effectiveness, as long as the wording did not claim or suggest that the product would cure, prevent or treat disease. A company could, for example, claim that a Saw Palmetto preparation "promoted prostate health".

The consumption of nutraceuticals and natural medicines has moved into the US mainstream. Andrew Weil, a physician and alternative practitioner has been featured on the cover of Time magazine and has a natural health website receiving several hundred thousand hits per month. On this site he prescribes an immune-enhancing diet containing several mushrooms related to those found in the forests of BC.

2.The Japanese and Asian markets for medicinal fungi and extracts - The Japanese market in l997 for nutraceuticals (of all types, not just mushrooms) was approximately US$ 4 billion. (KPMG l997). In Japan and other Asian countries, regulatory health claims are permitted, healthcare reimbursement for nutraceuticals is allowed and nutrition is stressed in medical curricula.

Close relatives of many fungi traditionally consumed and included in the Asian pharmacopoeia are found in the forests of BC and even the Japanese penchant for eating pine mushrooms is enhanced by their alleged longevity effects. Destructive gathering in Asian countries coupled with the effects of El Nino-exacerbated burning of Asian forests, which is continuing through l998, will decrease the supply in Asian countries of medicinal and nutraceutical mushrooms, creating scarcity in some species.
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To give specific examples, fresh or dried *Ganoderma spp.* and other species or refined extracts could be sold to a variety of concerns, including Canadian and offshore nutraceutical and pharmaceutical firms or research facilities at universities, North American health food and vitamin distributors, etc. and traditional preventative healthcare fungi are being increasingly consumed by a growing Asian middle class.

In general the most accessible and potentially profitable nutraceutical markets are those of the US, Japan, Germany, the Scandinavian countries, and Southeast Asia when it recovers from its current financial problems. In all of these areas product health claims can be legally made, and in both Europe and Asia, the use of botanicals is well incorporated into contemporary medicine and preventative healthcare.

Gunner (l998) summarizes three dominant barriers to marketing nutraceuticals (including nutraceutical fungi) in Canada – a restrictive regulatory climate (with the Canadian Food and Drugs Acts preventing any health benefit claims on food packages); expensive clinical trials, and the difficulty of obtaining patent protection. These matters are scrutinized in the policy sections.

V. Plant-Based Medicines and Nutraceuticals

Introduction

We shall begin by emphasizing this distinction between pharmaceuticals and herbal medicines: in general the former are based on a single "active ingredient" from, say, a plant, while the latter it is thought, depend on combinations of ingredients for their therapeutic properties. There is, however, a definite trend to standardize extracts from medicinal botanicals in terms of a single ingredient. The beneficial properties of St. John's Wort, it is thought, arise from the hypericin content, and preparations are

standardized in terms of the mgs. of hypericin per unit dosage.
If possible and commercially feasible, companies will synthesize the active ingredient for pharmaceutical medicines (in which case the source materials may no longer be needed), while with herbals, the entire plant, or some part of it, or a liquid or dry extract may be consumed Again, most active ingredients from natural sources are too complex or expensive to synthesize commercially.

Herbal medicines purified to certain stringent levels of standardized ingredients are called phytomedicines or phytopharmaceuticals. European countries have a long tradition of mainstream use of phytomedicines, and some of the main producing companies in Germany, France, Switzerland and Italy are 120 years old.

Botanical treatments for various conditions generally cost less than half of the equivalent pharmaceutical product –ten cents per day for valerian as a sleep aid, a dollar daily for a typical saw palmetto treatment for prostate problems.

Botanical herbs are typically sold not merely individually but as part of complex herbal formulae which sometimes contain non-herbal ingredients. The main product differentiation is now organic production through either growing or wildcrafting, and standardization of potency of ingredients. The best selling products are now standardized to a specific marker chemical or active component, and the production of botanical preparations is now approaching pharmaceutical grade quality control, especially in Europe where phytopharmaceutical formulae contain standardized extracts of Gingko, Saw Palmetto, Echinacea and such.

With the exception of the research on the medicinal effects of BC first nations botanicals, space precludes even a cursory review of the clinical and laboratory research on medicinal botanicals of the European pharmacoepia, which still comprise the bulk of medicinal herbs sold in North America. The reason we conducted such a review of medicinal mushroom research in the previous sections is that there is general ignorance of this work in Canada and the US since it has been largely done in China, Japan and the Russian Far East and published in foreign language journals which are seldom translated into English.

Nutraceuticals (things one eats to stay healthy or get healthier) have always been around and traditionally included vitamins, minerals, enzymes, and specialty supplements such as shark cartilage. In the past few years as North Americans have grown more sophisticated about the European experiences with herbal medicines, traditional nutraceutical products have been joined by a gamut of alleged immune-boosting herbals either gathered or grown. In North America where phytomedicines and the medical establishment are still at war, the awareness of work such as Germany's Kommission E monographs has been slow since most scientific publications on herbs and phytomedicines are published in European medical journals, often in languages other than English, since the destined target reading audiences and markets are in Germany, Italy and France.

The consumers of herbal medicines and nutraceuticals in Europe, and increasingly in North America, believe one can build up resistance to disease by regular nutraceutical consumption. They are better educated, have higher incomes and believe one can take control over one's health, and if North American physicians will not provide herbal medicines, increasingly these people are researching and providing their own phytomedicines and nutraceuticals over the internet.

But as yet BC and US herbal products manufacturers have generally restricted their product line to plants common in the European pharmacoepia -Feverfew, Oregon grape, Saint John's Wort, Echinacea, Burdock, Valerian, Gingko Biloba, Goldenseal, and such, and few BC nutraceutical or botanical producers have taken up many BC indigenous plants beyond Devil's Club, Oregon Grape and St. John's Wort. Nutraceutical manufacturers such as Sisu, (which have been experiencing around 30% annual revenue growth during the past two years) are understandably prudent about new product development and take up new "ingredients" only when there is a proven market plus substantial supporting scientific evidence about a botanical's effects in publications such as *Phytomedicine* And yet, with ingredients contained within this traditional European pharmacoepia, Sisu and several other nutraceutical firms we interviewed have introduced or are planning to introduce their own line of phytomedicines available to physicians only.

This industry of plant-based medicines and nutraceuticals is more complex than BC's mushroom industry because it has several components –the wildcrafters, the pharmaceutical companies located here-- some of which are bioprospecting for, testing, or manufacturing forest-based pharmaceuticals-- the medicinal herbs growers and the health food supplement and medicinal herbs products manufacturers (the nutraceutical industry). We begin this section with a brief review of the world markets for herbal medicines and industrial trends in these industries, and then analyze the BC pharmaceutical industry, the BC wildcrafters, and the provincial nutraceutical manufacturers – including markets, revenues, products, production technologies and related matters.

The World Markets for Herbal Medicines

The only countries in the world with significant prescription sales of phyto (plant) medicines are Japan, Germany, China and India. Most of the sales of herbal medicines in North America and Europe are OTC (over-the-counter) and are sold in the US as dietary supplements. These do not require a prescription. Germany comprises about half of the European phytomedicine market and Germany's per capita consumption of herbal medicines is about ten times that of any other European country.

The world market for herbal medicines (both crude extracts and refined, so-called phytopharmaceuticals) has been estimated as US $14 billion in l996 (Genetic Engineering News l997) – Europe - $7 billion, Japan - $2.4 billion, North America - $l.6 billion and the rest of the world - $3 billion. The leading European products in the first quarter of l998 were Ginkgo biloba, Ginseng, Garlic, St. John's Wort, Evening Primrose and Echinacea. Phytomedicine sales in Europe increased l0-15% in l997 compared to the previous year. By l997 Americans were spending US $27 billion annually on alternative treatments of all kinds (JAMA l998).

The most developed market is that of Germany ($3.5 billion) , France (($1.8 billion) and Italy ($0.7 billion). In European countries, and especially in Germany, a sophisticated consumer pre-disposition toward botanical drugs together with general acceptance by doctors of the use of medicinal botanicals has resulted in an open regulatory climate. Eighty percent of German doctors regularly prescribe medicinal herbs and their study is part of training for physicians.

Industrial Trends

Herbal medicines have long been part of the established medical practice in Germany. The German Medicines Act of l978 has permitted the issuing of Standard Licenses for botanical products after each has been examined in a published monograph which details qualitative and quantitative information about the product –side effects, interactions, dosages, effects, indications, contraindications, etc. These monographs are created under the jurisdiction of a specially conceived body called Kommission E of the *Bundesgesundheitsamt* (German Federal Health Agency) and the focus in the German system is on individual plants. Thus far four hundred and ten monographs have been created analyzing 324 herbs with recommended dosages and it is expected that this approach will be accepted by the EU. Of all the herbal medicines sold in Germany, about half are OTC products sold for self-treatment and the other half via medical prescription.

The recent action by the German government limiting ginkgolic acid levels in ginkgo leaf extracts illustrates the extent that herbals are incorporated into mainstream medical practice in Europe and the type of on-going attention to standardization that this requires. Standardized extracts of *Ginkgo biloba* have been long approved by Germany's Kommission E for circulation and related cognitive benefits. Kommission E's monograph for dry Gingko leaf extract specifies several parameters which must be in a certain range. For example, the herb/extract ratio must be within the range of 35-67:l and extracts must contain 22-27 percent flavonone glycosides and 5-7 percent terpene lactones, together with specific ranges of bilobalide and ginkgolides A,B, and C. Also ginkgolic acids must be less that five parts per million. This is because ginkgolic acids are classified as alkylphenols and are related to compounds found in poison ivy and associated with allergic responses.

Accordingly in May l997 the German Institute for Drugs and Medicinal Products informed all German manufacturers of Ginkgo extracts and preparations that the amount of ginkgolic acid in all gingko products has to be less than five parts per million., and that if proof of such cannot be offered, the registration for these products would be cancelled. (Herbalgram l997).

Since Europe is forging a common legal framework for botanical products, these can be sold as drugs with both labels and inserts. They can be legally prescribed by doctors and most importantly, expenses can be reimbursed through various medical insurance plans. Such is not the case in Canada, where only herbal laxatives can be partially reimbursed.

The cost of prescribed phytomedicines can also be reimbursed in France, but in the UK many phytomedicines are in a "General Sales List" category and are sold as food supplements without the possibility of reimbursement. Prescribed St. John's Wort costs can be reimbursed in Germany (and is sold also over the counter), while in France it is available only as an OTC drug and as a food supplement in the Netherlands. To harmonize these discrepancies, according to EU directive 65/65 soon all phytomedicines will be treated as drugs and necessitate registrations based on efficacy and safety. ESCOP (the European Scientific Cooperative for Phytomedicines) will prepare European monographs to be used as the foundation for registrations of phytomedicines in Europe.

When a phytomedicine is registered in one EU state, a registration holder can apply for recognition in other EU member states (which must respond within 90 days). In the case of an unresolved conflict, a central EU agency, the Committee for Proprietary Medicinal Products, will adjudicate and try to arrive at a decision which is binding on all EU members.

Until this year German herbal medicines could be sold in "apothekes", which also sell prescription drugs, in pharmacies which sell over-the-counter products and in natural food stores. But Kommission E was disbanded several months ago, and in-coming EU regulations, as noted, may require that botanical medicines either be treated the same way as chemical drugs or be sold exclusively as a "traditionally-used" drug.

In Germany, as in other countries, pharmaceutical multinationals are forging alliances with botanical medicine companies to participate in these trends. Bayer has collaborated with Zeller AG to market an herbal antidepressant alongside their chemical product and thus giving physicians the choice to prescribe the mild botanical or chemical product. In addition during the past decade there have been more than thirty acquisitions by large pharmaceutical multinationals of phytomedicine companies. For example Johnson & Johnson purchased Woelm Pharma (Germany); Rhone Poulenc Rohrer bought Natterman; SmithKline Beecham acquired Fink, and Boehringer Ingelheim bought the BC company Quest.

In addition to direct acquisitions, some multinational pharmaceuticals companies have taken to marketing phytomedicines produced by smaller companies – for example Ciba Geigy sells a phytomedicine line called "Valverde" made by Zeller AG of Switzerland, and BASF also sells Zeller products. Also Boehringer Ingellheim, Lederle and Schering all sell phytomedicines produced by Lichtwer Pharma.

One sees the same acquisition trends in the US, where botanical medicines are marketed as dietary supplements and are not regulated as drugs. In North America herbal medicines and nutraceuticals now carry trusted brand names and have moved into supermarkets, mass retail chains and drugstores. In April l998 Celestial Seasonings introduced a line of l7 herbal supplements including a St. John's Wort-based product called "Mood Mender". American Home Products is similarly about to release a line of products blending vitamins and herbs, and Bayer, producer of One-a-Day brand vitamins and minerals is about to release a similar line. Wal-Mart already sells herbal-vitamin blends near its in-store pharmacies under the "Spring Valley" name.

When big pharmaceutical companies are not acquiring manufacturers of herbal supplements, they are fighting them. For example, there is currently a court case in the US between the FDA and Pharmanex Inc., a manufacturer of a product called Cholestin, which is sold as an herbal supplement in Wal-Mart. The FDA and Merck & Company want to ban it because it contains a natural form of a key ingredient in a cholesterol-lowering drug made by Merck called Mevacor.
In the US, the Dietary Supplement Health and Education Act of l994 essentially created the industry of

nutraceuticals. Before that time there were only three food and drug categories – foods, dietary supplements and pharmaceuticals. Nutraceuticals in this law fall between dietary supplements and pharmaceuticals, and manufacturers are now allowed to make limited label claims to differentiate them from ordinary nutritional products. Under this Act, each FDA-regulated nutraceutical product falls into a particular regulatory class, and a higher classification merits more latitude in the statement of product benefits.

In the meantime since most herbal preparations in the US are still sold as dietary supplements, producers do not have to finance expensive research proving their products safe and effective, but at the same time they cannot make claims about cures. There is a widespread split of opinion in the US and Canada about regulation, with some favouring the German model with government-sponsored research providing the support for health claims on product labels and others opposing "government interference". However it might be claimed that the botanical products manufacturers in the US have made no significant industry-driven moves to gua rantee the purity or quality of their products. Most Canadian and US companies do not have their own standardization and control programs to identify the levels and purity of herbal ingredients in their products, Many North American manufacturers purchase only lowest-priced ingredients from China and other countries and accept dubious certificates of analysis from suppliers as the sole proof of quality.

Pharmaceuticals From Plants

There are two essential approaches to drug discovery – make them yourself or borrow from nature. – in other words rational drug design in laboratories by techniques such as combinatorial chemistry or looking for models from nature through screening of wildlands-based fauna and flora. In both approaches a sophisticated technological capacity is required.

There are also basically three ways raw fauna and flora can provide new medicines, preventative healthcare tonics, pesticides, fungicides or other products –they may be sold as dried or raw material, as extracts of various degrees of refinement or they may provide molecular models upon which to synthesize new drugs. (Most plant-derived drugs cannot be commercially synthesized). These ways indicate different segments of the BC industry involved with medicines from plants –various wildcrafters collect a variety of dried flora (at least 40 species) which are sold almost exclusively into US markets, and there are an increasing number of small pharmaceutical firms seeking to make drugs from BC flora, which they have often identified through reviewing the ethnobotanical literature – the study of what fauna and flora indigenous peoples use.

With *bioprospecting*, there are several ways to search for bioactive ingredients in fauna and flora – *randomly, taxonomically* (looking for plants in the same genus of a species known to contain certain active medicinal ingredients) or *ethnobotanically* (searching in only those plants and extracts traditionally used for medicinal purposes for hundreds of years by first nations). Another way is called *ecological* searching. One might, for example, observe leaves on the forest floor which do not decay and observe which insects lay eggs on it, analyze these eggs and find a new fungicide.

What we term "traditional use" by indigenous peoples should actually be called *prescreening*, because

this is precisely whit first nations have done over centuries, if not millennia, in testing medicinal plant preparations on themselves –this process has involved identification, preparations and removal of toxins, modifications, correlation of dosages with specific types of illnesses, and so forth. Through precise observation and human experimentation, first nations learned which plants and which parts to eat as medicines, and the optimal conditions for harvesting them.
When pharmaceutical companies search ethnobotanically (either by questioning elders or through review of the ethnobotanical literature), make, patent and sell products based on this knowledge with no compensations going to first nations, they are appropriating and using this knowledge in the same way people use pirated computer software. The fact that this knowledge has passed into the public domain through the publications of ethnobotanists and others is irrelevant to the legal claim of proprietary first nations' rights in traditional knowledge. These matters are taken up in the policy sections.

In random searching, the probability of discovering a commercially useful medicine from natural substances is about one in four million, and the entire process from searching to getting a drug through FDA or HPB approval in the US or Canada respectively may cost up to US $300 million and take ten years. But if a traditional medicinal or health mixture is sold as a food supplement or nutraceutical, it does not have to go through such regulatory hurdles in many countries. (This issue pertains to how BC industry can maximize revenues from forest-based medicines and nutraceuticals and is taken up in the policy sections).

This rate of randomly discovering a new commercial medicine is based on the following calculations: if a sample is randomly chosen, it has a chance of around one in one thousand to survive the first screening for a specific application. Of such hits, less than three percent will pass the testing for effectiveness and uniqueness and thus become a "lead". Only ten percent of all leads become candidate products, and of these only about fifteen percent eventually become commercial products.

It may take seven years for a sample to gain candidate status and another four to seven years to become a commercial product.

However with ethnobotanical searching, the probability of finding a bioactive compound which might (or might not) be medically useful, is about one in ten since the search domain is restricted to material which has been pre-screened and tested by indigenous peoples. *Nevertheless, the automated rapid screening technologies discussed in the next sections, which can facilitate the screening of tens of thousands of samples daily, will soon be cheaper than asking locals. When this happens, the large pharmaceutical companies which scrutinize natural products will cease ethnobotanical searches and return to random screening of everything.*

Ethnobotanists and ethnopharmacologists are also usually more interested in the entire chemical structure of the plant materials, which may actually yield the therapeutic effects, while random or taxonomic searches by pharmaceutical companies have concentrated on isolating a single active compound whose mechanisms may be understood with respect to a specific disease or pathology.
The scientific merits of such herbal remedies is a subject of continuing controversy. However from an economic perspective, it does not matter whether they work or not as long as people believe that they

work and buy them.
In any case, the strategy of new drug development based on leads from traditional sources (first nation's or Chinese herbs, say) has sometimes worked since it is guided by a long history of clinical practice. To give three brief examples, *Huperzia selago* (Fir Clubmoss) was traditionally used in both the pharmacopoeia of BC first nations and in traditional Chinese medicine. Huperzine A, an alkaloid isolated from leaves of the Chinese *Huperzia* species, is currently one of the most promising drugs for testing memory and learning loss in Alzheimer's patients and has been recently patented by the Chinese (S. Borman l993). Clinical trials in the US indicate that huperzine is considerably less toxic and more effective than tacrine, one of the few drugs currently approved by the FDA for Alzheimer's.

In another case, the root of a vine called *Radix pucrariae*, used for centuries in traditional Chinese medicine (and regularly consumed as a food) to treat alcohol abuse, was found to contain a substance called daidzin which suppresses the craving for alcohol in animals. (W.M. Keung *et al*. l995). Finally S. Lee-Huang and her colleagues at New York School of Medicine (l995) have isolated a protein, MAP 30, from another traditional Chinese medicine, bitter melon, and found that it had multiple anti-HIV effects. (The MAP protein is able to inhibit HIV-l integrase, one of the enzymes responsible for the virus's gene expression). This sort of activity is unique among anti-HIV agents and the development of integrase inhibitors is being vigorously pursued.
In all of these examples, although Western researchers sought and found single active substances, the source material was traditionally consumed as a food or nutraceutical (herbal preventative), and all three agents were identified through ethnobotanical searching.

For most pharmaceutical multinationals, the search for plant-derived medicines still comprises a tiny proportion of their entire budget. For example in the much-discussed agreement between Merck and Co. Inc. and Costa Rica's National Institute of Biodiversity, in which the latter organization screened plants, soil organisms and insects for bioactivity and made these available to Merck on a blind basis, only US $l million was paid in up front costs and an undisclosed but small portion of royalties on resulting commercial products.

One reason big companies have shied away from herbals is that the effects of such plant mixtures are often probably synergistic (result from the combination of several ingredients) and because of this the FDA will not license them. Western companies generally will not look for a mixture which has therapeutic effects because it cannot patent it. A related problem is that the herbal products industry has scant incentive to perform research since raw herbal products cannot be patented. The economic rate of return on private research investment is generally greater than that of government research, and the province should therefore investigate and devise botanical research incentives which address this problem. These matters are taken up in Part II.
In spite of this fact, many pharmaceutical and biotech companies continue to scour the forests of the world for new plant-based leads. Of the l20 or so main prescription drugs currently in use today (arising from only 90 plant species), an estimated 75% were located through ethnobotanical knowledge or folklore claims.

Underlying Production Technologies

Natural Products Chemistry

Bioprospecting is the systematic search for new applications of biological species. First collectors gather samples of biological materials in the field. Extracts are removed from these samples with solvents and then screened for medicinal effects. A very promising extract with pharmaceutical applications will be then partially purified and given a crude check for its chemical novelty ("dereplicated"). Active principles of the extract are then purified, dereplicated again and isolated, and extract structure determined. Such "leads" are consequently tested to determine the scientific basis for their activity, modified chemically to improve effectiveness and reduce toxicity and in the end given an extensive battery of tests for safety and effectiveness before being placed on the world pharmaceutical markets. The following discussion describes this process in more detail.

Preparation of Extracts

An extract is a solution produced by soaking dried plant or animal material in an appropriate solvent under controlled conditions. Such extracts are the raw material of bioprospecting. For a sample to be useful, its place of origin must be described so additional samples may be obtained when necessary.

The value of the sample to the prospecting client increases if it is accompanied by taxonomic or ecological clues concerning the identity of secondary metabolites (chemicals) which the source organism produces, or even more valuable, by ethnobotanical knowledge about traditional use. InBIO in Costa Rica in its collaboration with Merck and other companies has used a random screening strategy since they produce a large number of samples well-categorized in terms of ecology and taxonomy but which are chemically unpurified mixtures. This strategy is possible only because of recent technological innovations which make mass initial screening for new medicinal applications inexpensive and rapid.

These rapid screens rely on low-cost, computer-automated bioassays which mimic required pharmaceutical properties. Such bioassays can eliminate most of the samples and allow one to focus on the small minority which have actual prospects for commercial success. (The downside is that such rapid computer-automated bioassays will eliminate samples active in the specific application but which work on principles different from the specific one embedded in the bioassay).

Receptors are proteins which allow hormones or drugs moving in the bloodstream to recognize they have reached their target organ. In a normal screen, one wishes to determine whether any component of the extract inhibits a specific enzyme reaction or attaches itself to a receptor molecule which acts as a proxy for the organ being studied. Any molecule which will not bind to a receptor protein of a specific organ generally will not have a pharmaceutical effect on the organ.
Specific bioassays are chosen in terms of the commercial objectives of the company, and a lab in a large pharmaceutical firm will often use l0-40 screens, each one directed toward a different commercial objective. As new screens emerge from research and the firm's commercial objectives evolve, this gamut of bioassays may change yearly. A hit is confirmed by conducting a bioassay on another portion of the sample.

Fractionation and Crude Dereplication

Any confirmed hits from the rapid screening are then partially purified or "fractionated" and then subjected to further testing on animals and cells. The emerging pattern of their responses to these further tests is compared to known responses of a library of compounds. Such a crude dereplication prevents researchers from spending time and money in characterizing a compound which will probably resemble well-known molecules.

Purification and Characterization

Surviving "dereplicated hits" have still not been fully chemically characterized or purified. A company must still determine if the hits economically merit further investment necessary for purification and chemical characterization of the active principle molecule(s). A dereplicated, purified and fully chemically-characterized hit is called a "lead". Computer-automated enzyme and receptor screening, then, involves the computer automation of some of the above processes, but there is really no satisfactory computer-automated screening procedures for antiviral compounds (Jim Hudson, personal communication).

Product Development

At this stage the company identifies the mechanism(s) of pharmacological effects which were observed in the screening process together with any toxicological characteristics. More and extensive animal tests are conducted for safety and effectiveness and chemical modifications are usually introduced to increase the effectiveness of delivery. The company then attempts to synthesize the active ingredient(s) or guarantee reliable supplies of the source substance. Human testing begins and if the drug is to be sold in the US, such tests must be done in accordance with rigorous regulations specified by the US Food and Drug Administration.

Institutional Models for Bioprospecting

The well-known collaboration between Costa Rica's Institute of Biodiversity (InBio) and Merck & Co. is now not the only model for bioprospectng. (Merck paid an up-front fee for access to samples plus royalties on sales). In another case, Andes Pharmaceutical of Washington, DC, has been negotiating with the government of Colombia to access rights to that country's biodiversity. Andes is planning to set up a network of laboratories in Colombia to carry out proprietary screening for cancer. Colombia would get no fees for providing access but would receive royalty payments when one of its species becomes a commercial success.

In another case, Australia's Department of Conservation and Land Management has put out a call for proposals from companies interested in screening samples in its library of plant extracts, has commissioned the collecting and processing of further extracts and has established a screening facility in Western Autralia.

Combinatorial Chemistry

An alternative to the natural products testing described above is called *combinatorial chemistry*, the development of which is depressing the current prices paid for faunal and floral extracts throughout the world.

Combinatorial chemistry involves reacting some known molecule with many other chemicals to produce a mixture of plant-based derivatives with potential bioactivity. Combinatorial techniques apply the principles of parallel processing to medicinal chemistry and shift the laboratory design of new compounds from one molecule at a time to the automation of parallel synthesis. Beginning with one useful or promising compound or molecule, companies are using robotic techniques to derive hundreds of thousands of chemical variations of that lead. The consequent chemical diversity increases the probability that new compounds will react with a target such as a disease-causing molecule. Combinatorial techniques have resulted in new methods for the random synthesis of large numbers of different polymers for a given set of monomers. One variant of these methods provides "built-in locators" which facilitate hits being easily extracted from any heterogeneous screening mixture.

Big drug firms have been buying combinatorial companies – Lilly purchased Sphinx Pharmaceuticals for US $72 million. Dow bought Selectide Corp. and Glaxo Wellcome Inc purchased Affymax for US$533 million. (Glaxo is also searching in the wildlands of Asia for plant-based anti-inflammatory drugs). Most other large pharmaceutical firms have created in-house combinatorial chemistry efforts. Combinatorial chemistry was created about a decade ago when a startup drug discovery firm in San Diego, Affymax NV, used the technique to create libraries of basic protein-like molecules.

During the first half of the nineties, this new technology resulted in pharmaceutical companies shifting away from the traditional compound development method described above, and refocusing their drug-screening efforts away from natural products screening. SmithKline, for example, in the past had a large program for testing thousands of microbial extracts, plants and marine organisms, but is decreasing program investment and shifting toward the new techniques.
One of the main problems with plant collection and extraction procedures is that they are labour-intensive and expensive, and since most organic molecules cannot be synthesized at cheap, commercial levels of production, companies must continually worry if the compound is accessible and retrievable in sufficient quantities.

But in spite of the trend toward combinatorial chemistry during the first half of the nineties, during the last two years there have been dozens of small startup companies which are bioprospecting and screening plant and microorganism-based chemicals for therapeutics effects. Perhaps the best known of these, the US-based company Phytera, has been concentrating on viral and fungal infections, and neurological and heart diseases, and Vancouver-based Terragen has sought a variety of drugs from BC soil microorganisms

Phytera has pioneered two techniques which will probably be adopted by the other startups. Given the high throughput automated screening techniques which can presently scan up to several hundred thousand compounds per week, a problem in natural products testing now is supplying of samples fast enough. Traditionally this involved the slow processing of entire plants (drying and grinding them up, and extracting component chemicals). Phytera instead works with several thousand species of plant cells in test tubes, from which new promising samples can be grown. Plant samples from the wild can cost up to l00 times those produced from cell cultures (Economist l998), and working with plant cells facilitates the second technique –stressing the plant to coax it to produce chemicals it would not ordinarily produce in the wild, or if it were picked at the wrong time. Thus before constituent chemicals are extracted, plants are sometimes, baked , frozen, injected with hormones and subjected to extremes of light and darkness. This technique has paid off and one of Phytera's products, an antifungal called Sunillin was produced when a plant's cell cultures were infected with *Aspergillus* mould and *Candida.* Phytera then used combinatorial techniques to devise several thousand variants of the original extract, some as effective as the original but far less toxic.

Phytera is also bioprospecting in the oceans, and using the same techniques as for plants, has isolated a new compound called marinovir from a bacterium which dwells in the oceans around California, which is an effective anti-herpes drug. More importantly, both sunillin and marinovir work in different and new ways from similar drugs in their classes with important implications for combating drug-resistant viruses.

The BC Pharmaceutical Industry

We were able to identify 22 firms in BC's pharmaceutical industry. In general these firms produce human prescription drugs and human and veterinary non-prescription drugs, vitamins and nutraceutical supplements, vaccines and hormones.

The l997 revenues of the 22 firms was approximately Can. $58 million, and they employed 930 people last year. In terms of revenues this industry is about the same size at the present as BC's floral greenery sector.

The largest employers were Stanley Pharmaceuticals, QLT Phototherapeutics, Inex Pharmaceuticals, Quest Vitamins, StressGen Biotechnologies, and Stemcell Technologies.
Of these 22 companies, about a fifth have an in-house combinatorial chemistry capability (or access via their head office research facility offshore) and seven are actively involved in natural products discovery, screening, clinical testing or production. If we include oceans-derived products, more than half of the seven startups are UBC spinoffs Examples of spinoffs include Forbes Medi-Tech Inc., currently researching and developing cholesterol-lowering drugs and nutraceuticals from by-products of the pulp industry, which emerged from the work of UBC's James Kutney; Phytogen, a producer of paclitaxel, whose technology was developed in the UBC laboratories of Neil Towers; TerraGen, which evolved from the work of Julian Davies of UBC's Department of Microbiology and Immunology, and Kineteck, which came out of the laboratory work of Steve Pellech and his associates.

BC Public Research Effort

As is the case with BC's biocide industry, the research effort here lies mainly in the public sector. In the following sections, we profile two such research groups.

A team at the BC Cancer Agency (BCCA) and the University of Victoria is actively seeking funding to investigate pharmaceutical agents present in traditionally used medicinal plants and under-utilized tree species bark. The BCCA's unique screen would target traditionally used medicinal substances for varying types of steroid hormone activity which could then be utilized for a variety of diseases including rheumatism, cancer, acne and hair loss. They plan to screen plant extracts also for anti-proliferative, differentiation and chemopreventive agents to be used in both treatment and prevention of cancer.

The BC Cancer Agency has studied several natural compounds for more than a decade which exert effects through the aryl hydrocarbon and steroid receptors and which interfere with normal hormonal signaling. This unique screen was developed in the context of research on the role of environmental contaminants in prostate cancer and they wish to use it to screen BC native plants.
Secondly a group of UBC researchers are on the leading edge in the search for new medicinal compounds from natural sources. For the past fifteen years, J. Hudson, N. Towers and their colleagues throughout the province have focused on medicinal plants with anti-viral and antibacterial activity from the tropics. The group has purified literally hundreds of antiviral and antibacterial molecules and these researchers have developed novel bioassays for detecting antiviral activity. (Hudson l994, l994a). Neil Towers has published so many refereed articles in this field that even a partial listing would unduly extend the reference section and has now turned his attention to the analysis of BC indigenous plants.

Although there has been sporadic work in BC on identifying and characterizing active phytochemicals, a coordinated, methodical effort has never occurred, and most work conducted by BC scientists has occurred with tropical species and has been funded by the Canadian Centre for Bacterial Diseases and the Natural Sciences and Engineering Research Council.

BC Company Profiles

In the following sections, we profile four of the seven BC companies involved with pharmaceutical and nutraceutical products derived initially from indigenous wildlands substances. The prevalence of companies involved in some way with paclitaxel, initially from the Pacific Yew, illustrates how a single phytomedicinal discovery can spawn an entire web of companies. Many of these emerging biotech companies make money through licensing their initially developed products to big pharmaceutical companies, which are on the constant lookout for new medicines for their developed markets. These smaller biotech companies can innovate and finish initial product development more effectively than the large pharmaceuticals but the former lack the financial and marketing clout to advance initially-developed products through the regulatory hurdles and to market them. Most of these emerging biotech spinoffs show annual losses. This is to be expected during the first few years of their growth.

Unless otherwise specified, all of the estimates for world and regional markets and market growth for individual drugs, drug classes or precursors are taken from these interviews with the companies. These figures are continually tracked and well known.

Forbes Medi-Tech. With eighteen core employees and a market capitalization in excess of Can. $30 million, Forbes Medi-Tech is a Vancouver-based biotechnology company developing preventative healthcare and pharmaceutical products derived from forestry by-products. Forbes' core technology, developed by James Kutney of UBC's Dept. of Chemistry and licensed in l993, enables them to extract a proprietary mixture of phytosterols from a pulp-and-paper industry by-product called tall oil. Phyto (plant) sterols are naturally occurring substances found in plants which are structurally similar to cholesterol.

Although the company lost $454,397 for the six month period ending January 3l, l998, Forbes is widely expected to turn a profit by 2000 and has entered the hypolipidemic (cholesterol-lowering) drug market which has estimated worldwide l997 sales of approximately US$7 billion (Forbes website) and an annual growth rate of l0-l2 percent.

Forbes has obtained exclusive worldwide commercial rights to products which may be derived or developed from this technology in receipt for royalties of up to l.5% of gross revenues for a twenty year period. Typical of several emerging biotechnology companies, Forbes has adopted a *virtual corporate structure*, which means that all R&D is done by outside associates, and they have managed to significantly reduce expenditures through forging research alliances with central R&D institutions in Canada – including UBC, McGill University, and St. Paul's Hospital in Vancouver.

With their expertise in the area of phytosterols, Forbes has produced the cholesterol lowering drug Cardiorex, (US market of US $7billion in l997) and a cholesterol-lowering food additive called Phytrol (US annual market of US $8 billion). Other products include the steroid precursors AD and ADD (US $l billion annually in the US market) and higher value steroid products such as Progesterone, estrogenic hormones, and a female contraceptive. (collectively estimated US annual market of US $2-4 billion).

Forbes has received several grants from the BC Science Council and the National Research Council and has a number of US and international patents pending on their technologies and drug formulations, in addition to trademark protection for Cardiorex and Phytrol. Phytosterols are a well-developed, large market, but Forbes is the only company whose proprietary phytosterol formulation has both a nutraceutical use (Phytrol), and pharmaceutical use (Cardiorex).
In early l998 the pharmaceutical giant Novartis paid Forbes for an exclusive option to a worldwide license to either use or sublicense Forbes' plant-based sterol formulations for use in food and nutraceutical products. Novartis is planning to conduct additional clinical trials on the formulations in addition to the clinical trial completed by Forbes in l997.Novartis will incorporate the formulation into margarine, mayonnaise and salad oil. One element of the Novartis strategy is to more closely link its nutraceutical business with pharmaceuticals through such products.
The Forbes phytosterols act mainly through preventing the absorption of cholesterol into the bloodstream and can be added to any foods containing fat such as margarine, yoghurt, ice cream, salad dressing, mayonnaise and such. If Phytrol were targeted mainly as an ingredient in margarine it would be tapping into a worldwide market of US $8 billion annually in the developed world alone.

Both Cardiorex and Phytrol have quite similar compositions with respect to phytosterol content, but Phytrol has been especially formulated to be added to foods, while Cardiorex is a pharmaceutical under study for cardiovascular problems. But both formulations have been found to lower the LDL plasma (bad) cholesterol, and has been shown in animal testing to prevent and delay the development of atherosclerotic lesions. Human trials at McGill University of persons with elevated cholesterol levels have yielded promising results, and Forbes has prepared an IND (Investigative New Drug) application to both the Canadian Health Protection Branch and the US Food and Drug Administration for approval to start clinical trials during l998.

Several researchers are trying to determine the mechanisms involved with Forbes phytosterol formulation with respect to lipid-lowering properties, but the therapeutic effects of (this essentially herbal) plant-based mixture may be complex and arise from a combination of ingredients and biochemical events. The formulation contains a pre-determined ratio of different types of phytosterols, and when eaten, these compete with the absorption of dietary cholesterol and enteric bile cholesterol reabsorption and possibly improve the chylomicron transport.
Similar to the alliance between Forbes and Norvartis, last year Johnson & Johnson purchased the worldwide marketing rights to Benecol, another cholesterol reducing product of Raisio Group of Finland. Benecol margarine has been available in Finland since l995 and is produced from a phytosterol derived from pine trees. Both companies are actively seeking new foods as carriers of their nutraceutical ingredients. Clinical studies published in the New England Journal of Medicine have indicated that if 25 grams of the Benecol margarine are consumed daily for six months, the typical reduction of blood cholesterol is around l0% (NEJM website). This is l0 times the average consumption of plant-based sterols in the typical North American diet. The Benecol margarine will come onto the North American market in the second half of l998.

The so-called *kraft* process in BC's pulp and paper industry involves cooking wood chips with an alkali such as sodium hydroxide to obtain a high quality pulp to mainly be used in the manufacture of paper. Unfortunately this process yields a high percentage of residuals in the form of a black liquid, and crude tall oil is one of the two main commercial by-products extracted from this black liquid. The tall oil is separated from the water and extracted through skimming.

BC's pulp and paper industry produces huge quantities of tall oil, the percentage of which depends on the species and geographical location of the forest from which the wood was taken. A typical yield of tall oil from a BC kraft mill might be around 50 kilograms per tonne of pulp in northern BC. Hardwoods yield small quantities of tall oil, while spruce or pine might typically yield one hundred kilograms per tonne of pulp. About 90% of the tall oil soap has no commercial value in crude form and is usually burned or dumped at cost. The remaining l0% is usually fractionated through vacuum distillation with about one million tonnes produced annually worldwide and used in the production of soap, paint, lacquers, and such.

Forbes became interested in tall oil mainly because it contains phytosterols such as b-sitosterol which can be used for the production of steroids otherwise produced from cholesterol. Forbes core technology involves a cost-effective method to extract phytosterols from tall oil and use these as inexpensive core material to manufacture pharmaceutical steroids and lipid-lowering drugs.

A typical Forbes phytosterol product is over 98% pure and comprises b-sitosterol, campesterol and stigmasterol. In the gastrointestinal tract phytosterols compete with cholesterol for receptor sites and therefore inhibit the uptake of the latter.

In addition, phytosterols, through well-developed fermentation techniques, can be transformed into androstenedione (AD) and androstadienedione (ADD), which are essential intermediaries for the synthesis of pharmaceutical steroids, and Forbes core technologies present a commercially attractive alternative process to yield such pharmaceuticals.

Both AD and ADD are central steroid pharmaceutical intermediaries used in the manufacture of oral contraceptives, anti-inflammatories and hormones, and the choice of sterols as raw material for the manufacture of AD/ADD depends on market conditions and availability. Thus most North American b-sitosterol production is derived from soy by-products while non-vegetable sources are utilized in Japan.

The world market for AD/ADD exceeds US$l.0 billion annually, with around 98% of AD/ADD in the US being derived from soy bean and only around 2% from various sterols. However the technology and cost advantages of Forbes are these: A Forbes proprietary *Mycobacterium* strain used in bioconversion processes reportedly has superior catalytic and physiological functions than the competition, (Searle, Schering and Upjohn), thus lowering overall production costs, and sterols from soybeans must be at least 90% pure to remove substances which interfere with fermentation, while sterols from tall oil have be only about 70% pure. Also it requires three separate extraction processes to remove sterols from soybeans while the Forbes process requires only a single stage.

With respect to cost, a kilogramme of 98% pure AD is currently priced at about US $l50, and the Forbes-derived source, tall oil costs only around US $l00 per metric tonne (compared with soybean oil which sells in the range of US $400-500/tonne). Forbes products are therefore based on abundant and comparatively inexpensive starting materials. Forbes has made an industrial alliance with Slovakofarma, a Slovakian public pharmaceutical company to extract phytosterols from tall oil and with Antibiotic Co. of Bulgaria to transform the sterols into bulk AD/ADD.
Having transformed their core AD/ADD technology to industrial partners, Forbes researchers have been concentrating on other commercial opportunities within the area of pharmaceutical steroids – including norethindrone, a generic female contraceptive. Pricing is a basic issue in this highly competitive market, and Searle has entered the Canadian market through offering *Select*, a contraceptive with norethindrone at 60% the price of other oral contraceptives on the market.
Ninety percent of the lipid-lowering US drug market of US $6-8 billion annually is dominated by the statin drug class which inhibits a crucial enzyme in the biosynthesis of cholesterol. This market has shown a compound annual growth rate of l2.4 percent during the last four years. This class of drugs demonstrates toxicity during long term use. Such is not true of Forbes' phytosterol formulation, which, in addition to having lipid-lowering properties, may also both inhibit and reduce atherosclerotic plaque in blood vessels. In this sense they have the superior product on the market.

TerraGen Diversity Inc. emerged in l996 from the West-East Centre for Microbial Diversity. This Centre itself was formed in l994 as a collaborative research venture between the University of British Columbia and the National University of Singapore. Potential commercial discoveries by this collaboration led to the formation of TerraGen with financial support from venture capital groups in both countries.

Their approximately thirty employees include eleven Ph.D.s and sixteen technicians, and the company

itself occupies 12,000 square feet of lab space in the Gerald McGavin building at UBC.
TerraGen's investors in their l997 private offering of Can. $10 million included MDS Capital Crop., SR One Ltd. (SmithKline Beecham's venture capital company), the Business Development Bank of Canada and the Singapore company, Technology Development Fund Pte. Ltd.
The exploitation of micro-organisms in the soil, lakes and rivers, ground water, oceans and sediment as sources for new pharmaceuticals, bioremediation processes and industrial chemicals has just begun, with less than l percent of all microbes being even identified. This is partially because the remaining 99 percent are difficult or impossible to cultivate under laboratory conditions.

Living organisms are good at producing bioactive molecules and for the past two decades, scientists have had considerable success in isolating single genes from microbes and "expressing" them in yeast or mammalian cells. Still, less than one percent of the millions of microbes in a handful of soil could be cultivated in the laboratory. TerraGen discovered that fragments of DNA could be extracted from uncultivable microbes and could be spliced into more amenable varieties of microbes to produce proteins, enzymes and peptides, and this company represents the next generation of combinatorial chemistry since it can extract large pieces of DNA from hitherto unexplored sources, engineer these into surrogate fungal or bacterial hosts to produce new chemicals.

TerraGen has thus developed a unique technology which eliminates the need to isolate pure cultures through eliminating a need to grow microbes from the environment. Through techniques of "combinatorial biology" they are able to isolate genetic material from unknown microbes which are difficult to cultivate and to clone their DNA into cultivable strains. Such "surrogate hosts" can be easily grown in the lab to facilitate cloning, screening and production of biochemicals which form the basis of unique "small molecule" natural products. Terragen has compiled libraries of DNA fragments over the years from soil samples in BC and around the world and has developed unique technology to extract large (l00 KB and greater) DNA fragments from a variety of environmental sources. Such is significant because the small molecules comprising secondary metabolites are often the products of "biosynthetic pathways" which contain many genes and can involve as many as thirty or forty enzymatic reaction stages.

The company is also one of the few to focus on the use of genetic material in lichens, of which there are in excess of l2,000 known species. Lichens are impossible to grow in the lab and thus until now they have provided almost no commercial uses. Lichens contain two or more organisms – a fungus and a cyanobacterium or an alga, or both. These component organisms engage in complex intracellular signaling and through inserting DNA fragments from lichens into fungal hosts such as A*spergillis sp.,* TerraGen is able to screen for bioactive products produced by lichens such as protein kinase inhibitors (chemicals which can be used to target the pathways of signal transductors). Lichens thus have the potential to produce a gamut of new metabolites with pharmaceutical value.

TerraGen's capacity to harvest the "genome complement" of microbes is providing lead compounds for further pharmaceutical development. Microbes from any environmental source – deep sea thermal vents, lichens, or BC temperate forest soil, can be explored for novel genes. When necessary, specific groups of microbes can be enriched to target specific sorts of pathways, and high molecular weight,

highly purified DNA is extracted and comprises the entire "biosynthetic potential" of entire microbial communities. Complex DNA pools or specific genes are identified for the production of primary libraries, which allow TerraGen to permanently store genetic information. Such libraries are then transferred into industrial microbial hosts where the genes are expressed, resulting in the production of novel secondary chemicals and active enzymes.
In addition to their collaborative screening programs with their industrial partners, TerraGen also conducts in-house screening based on whole cell assays to screen for antifungal and antimicrobial agents in addition to signal transduction modulators.

TerraGen is also planning to exploit the full biochemical potential of microbes to produce naturally-occurring pesticides and herbicides via direct access to DNA from microbe populations and novel genes which encode useful enzyme characteristics, and the flexibility of surrogate hosts will allow TerraGen to produce a variety of enzymes and molecules with varying physical characteristics (such as sensitivity of heat and cold or acid/base resistance) for use in industrial processes and in bioremediation.

In December l997, TerraGen scientists reported in *Antimicrobial Agents and Chemotherapy* (l997) that disease-carrying bacteria can develop resistance to antibiotics without ever having been exposed to the drugs. Recently some bacteria's resistance to antibiotics has become a worldwide problem and until now it was commonly believed that actual resistance occurred only when the bacteria was exposed to antibiotics in humans or animals and developed genetic mutations. But the TerraGen team reported the discovery of microbes with resistance to fluoroquinolone "due in part to natural DNA sequence variation." Thus all of their soil-cultivated microbes had not been previously exposed to fluoroquinolone, and an analysis of the bacteria's genetic structure revealed a highly variable gene called gyrA. The team speculates that natural variations in this gene present the bacteria a "coincidental resistance" to fluoroquinolone and that the methodical genetic analysis of bacteria will become a valuable scientific tool "in predicting mechanisms of bacterial resistance."

Since l995, Terragen has been collaborating with researchers at BC Research Inc. in an FRBC-supported project to characterize the microbial biodiversity in BC forest soils and to learn how these vary under different timber cutting practices (Axelrood l996). The biodiversity of bacterial soil communities is largely uncharacterized and it is estimated that less than one percent of the total soil population is cultivable. This team has used molecular approaches to characterize cultivable and uncultivable bacterial diversity in surface organic matter, mineral soil and lodgepole pine rhizosphere soil samples from treatment plots representing operational forest practices from the BC Ministry of Forests Long-Term Soil Productivity sites in Williams Lake, Smithers and Prince George, BC.

To generate revenues, TerraGen has created large polygenomic libraries in surrogate hosts and enters into collaborative agreements with big pharmaceutical and biotech companies throughout the world to screen TerraGen's libraries for bioactive compounds, signing one such agreement with Schering-Plough at the end of l998. Terragen receives financial returns in the form of licensing and milestone fees and royalty payments. Terragen does not release financial data.

Angiotech Pharmaceuticals, Inc., since its start in l992, has been engaged in developing and commercializing new treatments for chronic inflammatory diseases and has created a unique reformulation of the anti-tumour drug paclitaxel (first derived from the Pacific Yew tree) for new uses such as restenosis, rheumatoid arthritis, multiple sclerosis, psoriasis, surgical adhesions, inflammatory bowel disease and neovascular diseases of the eye. The estimated world market for paclitaxel formulations in l997 was US$ 941 million.

Angiotech's R&D activities, capital and operating expenditures and technology acquisitions have been funded mainly through private and public equity offerings, and in July l997, the company entered into an exclusive licensing agreement with two leading international manufacturers and distributors of medical devices for worldwide rights to develop and market paclitaxel-coated stents. The company has estimated that the agreement (equity investments, royalties and milestone payments) has a total value of around Can. $32 million. Angiotech had a net loss in l997 of Can. $5.9 million.

Angiotech's lab and administrative offices are situated in the Research Station Building of UBC and the company's work force of thirty five persons includes fifteen who hold advanced degrees in business and science and eight Ph.D.s. Of the total workforce, twenty employees are engaged in R&D, and the company has filed over thirty Investigational New Drug Applications with the US FDA and taken five pharmaceuticals through to product licensing applications.

Angiotech's basic technology came from a discovery of hitherto unrecognized mechanisms of action of paclitaxel -- that it is a strong inhibitor of angiogenesis and other processes involved in developing chronic inflammation. It is thought that paclitaxel has an ability to inhibit a key regulator, AP-1, of various genes, including those involved in tissue destruction and cytokines associated with chronic inflammation. Angiotech's scientists believe that paclitaxel operates through preventing AP-1 from initiating gene transcription characteristic in the progression of several degenerative and inflammation diseases.

It is thought that paclitaxel inhibits chronic inflammation through inhibiting the activity of white blood cells involved in initiating inflammation; reducing the production of enzymes which permanently damage tissue; and inhibiting the growth of blood vessels which service damaged tissue.

The other component of Angiotech's technology involves using "polymeric carriers" for drug delivery vehicles and the company produces a polymeric formulation of paclitaxel.
Having identified the ability of paclitaxel to act as an effective agent in chronic inflammatory diseases, the company produced a paclitaxel formulation without the allergenic additive, Cremophor EL, normally in Taxol formulations.

Rheumatoid arthritis is a progressive, chronic inflammatory disease affecting two percent of the world's population. There is a greater mortality rate with advanced rheumatoid arthritis than there is for many forms of cancer. The annual work market for antirheumatic agents (against rheumatoid arthritis) is estimated to be US $600 million and is growing at an annual rate of l4.5%. Anti-cancer drugs (mainly methotrexate) are currently the main therapy for the majority of rheumatoid arthritis patients, but Angiotech believes that this market offers major opportunities for its products. In various research collaborations, their scientists have found that paclitaxel impairs several processes involved in the progression of rheumatoid arthritis and that it can prevent some forms of joint damage.

Angiotech has also demonstrated that paclitaxel can be an effective treatment of multiple sclerosis. MS is the most prevalent form of neutral inflammatory disease and affects 400,000-500,000 persons in North America. The causes of MS are unknown but it is thought to be an auto-immune disease. Like rheumatoid arthritis, MS is characterized by inflammatory white blood cell infiltration, inappropriate proliferation of cells and secondary tissue destruction after enzyme release – all of which paclitaxel may inhibit. The estimated l997 world market for MS preparations is US $730 million.

The leading medications for MS, costing around US $10,000/year, are Avonex, a recombinant human beta interferon marketed by Biogen and Betaseron, a similar product of Berlex Laboratories, Inc. and a product marketed by Teva Marion Partners. However Angiotech's collaborative research with UCLA partners examined paclitaxel's ability to inhibit MS symptoms in transgenic mice and found that those treated with paclitaxel at the beginning of disease symptoms remained stable and in remission during the experimental period. Their data suggests that paclitaxel's inhibitory effects on MS arise through decreasing the proliferation of astrocytes (which are involved in demyelination in MS). Angiotech is currently conducting collaborative clinical trials with highly reputable institutions throughout the world of the effects of paclitaxel on MS and rheumatoid arthritis patients.

Phytogen Life Sciences Inc. is a manufacturer and supplier of high quality paclitaxel. This company was founded in l990 to develop and manufacture pharmaceuticals derived from natural sources and to date has developed an efficient, commercial scale production process for paclitaxel, extracted from the Pacific yew tree. Since its inception Phytogen has financed its operations mainly through debt financing, private equity issues and tax credits. Upon completion of their current offering, the company will have a capitalization of Can. $20,612,144. Phytogen's basic technology platform was conceived and developed by Neil Towers at his UBC laboratories.
Paclitaxel is currently approved in over sixty countries to treat ovarian and breast cancer, and as it proves effective in other forms of diseases such as non-small cell lung cancer and AIDs-related Kaposi's sarcoma, demand is growing and this year sales will probably exceed US $l billion. BMS held the exclusive US rights to manufacture paclitaxel until December l997, and since these rights have expired, Phytogen is attempting to become a leading world supplier. Phytogen is the only Canadian company which has submitted Drug Master Files for paclitaxel production with the FDA and the HPB.

With twenty five employees, Phytogen has a 22,000 square feet manufacturing facility on Annacis Island and through agreements with forestry companies and commercial growers has ensured a long term supply of raw yew materials. Much of their raw materials is sourced from contract growers in China.

They see two markets, the traditional pharmaceutical manufacturers which have a high current demand for paclitaxel, and the emerging herbal medicine/nutraceutical manufacturers. Phytogen can currently annually produce up to sixty kilograms of paclitaxel with an estimated current market price per treatment of US $4,500, or an annual value of US $270 million.

The company's Annacis production facility is run in accordance with the US regulatory requirements called Good Manufacturing Practices for pharmaceuticals and in June l998, Phytogen completed its pre-approval production inspection by the US FDA and the Canadian Health Protection Branch. Both agencies have subsequently approved Phytogen as a producer of paclitaxel which is in compliance with GMP guidelines.

Although predominately a manufacturer of paclitaxel for the generic short term markets, Phytogen continues to conduct new product searches of possible phytopharmaceuticals ingredients and is concentrating on traditional Chinese medicine. They are also anticipating filing a US patent application for a novel method of producing etoposide. This substance, widely used to treat venereal warts and testicular cancer, is derived from podophyllotoxin found in *Podophyllum peltatum*, which grows in eastern Canada but not in BC.

Phytogen has forged two significant paclitaxel strategic license and supply agreements with Mylan Pharmaceuticals, Inc in the US (market capitalization of US $3.9 billion) and Sinphar Pharmaceutical Co. Ltd. of Taiwan. Mylan anticipates gaining regulatory approval to market generic paclitaxel products in the US, Mexico and Canada by l999 and will source Phytogen's bulk paclitaxel for final dosage formulation. Mylan and Sinphar will pay Phytogen fifty percent of all net profits from their sales of final dosage paclitaxel after deducting certain of each parties' costs, and Mylan and Sinphar has agreed to purchase paclitaxel exclusively from Phytogen and are in turn responsible for product formulation, registration and distribution.

Through its experience in the manufacture of high quality paclitaxel, Phytogen is well-placed to manufacture and supply other natural ingredients to herbal medicine and nutraceutical manufacturers, whose production techniques will soon require pharmaceutical grade quality. If its long term consumption does not prove harmful, one can imagine, for example an herbal botanical formulae sold with paclitaxel in it.

Building on its core competence in producing low cost paclitaxel and etoposide in regulated pharmaceutical markets to generate short term revenues, Phytogen is also poised to satisfy the growing demand of the phytopharmaceutical sectors for contract manufacturing services.
Given their growth and employment potential, all of these companies merit significant provincial government support in the form of tax/fiscal incentives and programs, which until now have been limited to the discovery/research phase of drug development. These matters are examined in the policy sections of Part II.

Ethnobotanical Clues for BC Medicines and Nutraceuticals

Summary

The first comprehensive laboratory screening of British Columbian medicinal plants used by first nations peoples occurred in the early nineties when McCutcheon (l992) and others at the University of British Columbia began screening 96 plants traditionally used for antibiotic activity. (The vast majority of medicinal plants used by BC first nations belong to the Angiospermae and Gymnospermae, and in spite of the fact that BC has a rich biodiversity of fungi and mosses due to its climate, few of these plants were utilized by first nations as medicines).

Plants traditionally used medicinally by BC first nations were selected from the ethnobotanical publications of Nancy Turner and screened against eleven bacterial strains. Eighty five of the assayed extracts had significant antibiotic activity against two or more bacterial strains. Plants were categorized according to traditional use into six groups: potential antibiotic, general tonic, unspecified medicine, non-antibiotic medicine, and two non-medicinal categories. Ninety five percent of the plants categorized as potential antibiotics according to traditional use, exhibited significant antibiotic activity, and seventy five percent of these were found to be active against methicillin-resistant *Staphylococcus aureus*. Extracts with the widest spectra of activity were *Alnus rubra* bark and catkins, *Fragaria chiloensis* leaves, *Moneses uniflora* aerial parts, and the branches of *Rhus glabra.* Nine plant extracts were also found to be effective against *K. pneumoniae*, *S. marcescens*, and *P. aeruginosa* –all of which are resistant to current antibiotic therapy.

In more recent work, including her unpublished doctoral dissertation (l996), McCutcheon screened a hundred methanol plant extracts for antibiotic activity against *Mycobacterium tuberculosis* and *Mycobacterium avium.* Sixteen extracts of plants traditionally used by BC first nations (and again identified through three ethnobotanical works of Nancy Turner (l974, l980, l990) for the treatment of tuberculosis exhibited antibiotic activity, and extracts from *Heracleum maximum* (*Umbelliferae)* roots, *Moneses uniflora* (*Ericaceae)* aerial parts, and the inner bark of *Oplopanax horridus* completely inhibited the growth of both organisms. The growth of both organisms was also completely inhibited by *Alnus rubra* and catkins, *Empetrum nitgrum* branches, *Glehnia littoralis* roots and *Lomatium dissectum* roots.

Three of the extracts with the greatest activity against mycobacteria were all members of the same family: Umbelliferae: these were *G. littoralis, L. dissectum,* and *H. maximum.* In total, approximately one third of traditional first nations TB medicines assayed exhibited *in vitro* antimycobacterial activity, and although *in vitro* activity does not necessarily indicate *in vivo* effectiveness, these researchers are continuing to determine if equivalent results can be obtained from cellular assays.

This work is significant since TB is still the leading infectious killer throughout the world with about three million deaths annually, most of which are in the developing world. At the same time the incidence of TB in Europe and North America is again increasing. Both *Mycobacterium tuberculosis,* and *M. avium* cause disease especially in immuno-compromised hosts such as AIDS patients. (Forty percent of all cases of HIV are co-infected with *M. tuberculosis*, and TB is thus the main opportunistic infection of AIDS patients throughout the world.) As noted several treatments have developed natural resistance to the commonly used antimycobacterial drugs. (Some strains of TB are now resistant to seven of the most effective drugs available). At the same time the incidence of TB among Canadian first nations peoples is more than ten times higher than in the general population (Young and Casson, l988), and there is a pressing need for effective, new antimycobacterial drugs for people with these bacterial infections. Although there are literally hundreds of references throughout the ethnobotanical literature on first nations TB treatments, almost none of these until now have been assayed for antimycobacterial activity.

In other instances of compounds isolated from traditional first nations' medicinal plants, H. Matsuura *et al*. (l996) found significant antibacterial and antifungal properties of polyyne compounds from *Glehnia littoralis* spp. *leiocarpa*. This perennial herb which grows on sandy BC beaches was used by the Haida for the treatment of bladder infections and other ailments (Nancy Turner, personal communication). Matsuura *et al*. (l996a) have also identified an antibacterial thiophene from *Balsamorhiza sagittata*.

Antimycobacterial polyynes of Devil's Club (*Oplopanax horridus*) have also been examined by M. Kobaisy *et al*. (l997), who isolated two new polyynes with significant anti-*Candida*, antibacterial and antimycobacterial activity, including the ability to kill *Mycobacterium tuberculosis* resistant strains of *Mycobacterium avium* at l0 microgram/disk in a disk diffusion assay. Devil's Club was traditionally used by almost all BC first nations peoples against a wide range of afflictions such as diabetes, rheumatism, colds, headaches, TB and lung haemorrhages.
Searching for TB therapeutics is much more dangerous than most antibiotic development programs, since the airborne TB pathogens are so virulent that special containment facilities and procedures must be used, and other bacterial genera cannot substitute for antimycobacterial screenings since the waxy coat which renders *Mycobacterium* impervious to being destroyed by white blood cells, also acts as an impenetrable barrier to many antibiotics. (McCutcheon *et al.* 1997).Any real leads therefore are of value.

In addition to the above researchers, several other BC academics, and their colleagues at other universities, as previously discussed are in the vanguard of the search for new pharmaceutical agents from both tropical and BC wildlands sources. For example, Robert Hancock and Neil Towers (UBC), funded by the Canadian Bacterial Diseases Network, have also been characterizing medicinal plants used by BC first nations peoples for anti-fungal and anti-bacterial activities and a second group of plants for anti-tuberculosis, anti-viral, anti-protease, anti-virulence-factor secretion and immune-enhancing activities (Towers *et al.* in press). James Hudson and Neil Towers, as noted, have an on-going project screening anti-viral plants from tropical areas, and this group has developed several new techniques of bioassays for detecting compounds with anti-viral activities. Geeta Saxena *et al.* (l996) recently isolated a new antibiotic, Chlorochimaphilin, from *Moneses uniflora,* another first nations cough medicine traditionally used by the Thompson as recorded by N. Turner.

Most significantly the UBC group is exploring the hypothesis that the benefits of some medicinal plant extracts arise from additional compounds aside from those with direct anti-viral activity. Such compounds may represent "indirect" anti-viral activities and are mediated by the actions of cytokines (active molecules which control immune responses) (N. Towers personal communication). The importance of this work arises from a recent research hypothesis that there exists a "cytokine network" which must be in balance for proper resistance to infecting agents. It has been found that many viruses alter the levels of certain cytokines, thus decreasing the host responses and leading to chronic infection. Assuming that certain phytochemicals might work through restoring this "cytokine balance", both plant extracts and extracted bioactive compounds are being assayed for their effect on cytokine gene expression. This group of UBC researchers, which is considered to be a Canadian national treasure by authorities and the private sector in most countries, has difficulties in obtaining funds domestically.

A Methodical Screening

In spite of above research, by the mid-nineties, only a tiny percentage of traditionally used North American medicinal and nutraceutical plants had been screened by modern science. This tiny percentage concentrated almost entirely on anti-cancer agents and three emerged – etoposide from *Podophyllum peltatum* (Mayapple), taxol from *Taxus brevifolia,* and betulinic acid from *Betula alba* (birch tree). A tea made from T*axus brevifolia* was widely consumed by BC first nations peoples as both a medicine when sick—for example the Haida drank it for certain forms of cancer and as a nutraceutical – yew tea was regularly drunk by the Haisla as a heart medicine (Nancy Turner, personal communication). In her unpublished doctoral dissertation, McCutcheon (l996) has conducted the first comprehensive *in vitro* evaluations of anti-infectious properties of prescreened first nations plants from western North America.

McCutcheon methodically screened one hundred methanolic plant extracts for antibiotic, antifungal, antimycobacterial and antiviral activity. Most of these plants were chosen because of traditional medicinal and other use by BC first nations peoples. Eighty nine of the extracts showed antibiotic activity and eighty one antifungal activity. Nineteen exhibited antimycobacterial activity, and twelve extracts were active against one of seven viruses screened. Drug resistant strains are rapidly overcoming contemporary treatments of bacterial infection, and most recent leads have emerged from soil microorganisms. But this source is again being supplemented as attention has now shifted again to plants as humanity's original and primary source of antibacterial agents. At the same time there is a growing number of immunosuppressed persons with life-threatening fungal infections in developed countries and an increased demand for systemic antifungals. Also, as noted, new antimycobacterial drugs are immediately required to treat the resurgence of TB, exacerbated by secondary TB infections in AIDS patients.

The least progress by pharmacologists lies in the area of antiviral development, because few people in developed economies die from viral infections and the general similarities between human and viral chemistry inhibit developing safe therapeutics. However the AIDS epidemic has accelerated antiviral development. Even so, many viral infections remain impervious to treatment and the hundreds of pre-screened remedies by first nations peoples provide a promising source of new treatments.

Prior to McCutcheon's work, the traditionally-used medicines of BC's first nations had not been methodically investigated, although the eminent North American ethnobotanist, Nancy Turner, and other ethnobotanists have extensively studied their source plants and traditional uses. The hundred plant samples analyzed by McCutcheon were selected from the several hundred mentioned in *Thompson Ethnobotany* (Turner, l990), *Ethnobotany of the Okanagan-Colville Indians* (Turner l980), and *Plant Taxonomy and Systematics of Three Contemporary Indian Groups of the Pacific Northwest* (Turner l974). The plants listed in these sources plus those in the appendices of (McCutcheon l997) are the "best economic bets" for further screening. McCutcheon's screening just scratches the surface.

Summary of Screenings

McCutcheon found a significant correlation between antimycobacterial activity and the traditional use of plants to treat tuberculosis, and significantly higher percentages of traditionally used plants were found to be potential medicines. There also appeared to be correlations between activity and the active plants' taxa and habitats from which they were collected.

In the second part of this work, seventy seven percent of all extracts showed antibiotic activity and three quarters of plants which were traditionally used as medicines were active. Of all plants classified as potential antibiotics based on traditional usage, ninety one percent were active, and the taxa with the highest percent of active extracts were the Filicinae and Gymnospermae.

Fifty nine percent of extracts showed significant activity in antifungal screening, and the taxon with the highest percent of active extracts was the Gymnospermae. Seventy five percent of plants classified as potential antifungals based on traditional use were shown to have significant activity.
Since throughout the two phases of screenings, members of the genus *Artemisia L.* were found to have a broad spectrum of activity, this genus was chosen for additional research on anti-infectious properties of seventy four additional samples representative of 30 Artemisa taxa. All of the *Artemisia* samples showed antibiotic and antifungal activity, and in antiviral assays, eighteen extracts inhibited virally-induced cytopathic effects. The *Artemesia* species most frequently cited in ethnobotanical literature (*A. dracunculus*, *A. frigida, A. ludoviciana*, and *A. tridentata*) were among the most active extracts in all assays.

For each individual screening, a thorough ethnopharmacological analysis was conducted based on a nearly complete review of traditional medicinal uses in all available ethnobotanical literature.
In part I, the antibiotic assays, for each major taxonomic division (Eumycota, Thallophyta, Bryopsida, Sphenopsida, Lycopsida, Filicinae, Gymnospermae and Angiospermae), the total number and percentage of active extracts were calculated. The collated ethnopharmacological data which summarized traditional medicinal uses of the plants was utilized as a basis for ethnopharmacological classifications. Extracts traditionally used to treat bacteria-caused ailments were assigned to the category "potential antibiotics". Extracts of plants used traditionally to treat illnesses possibly caused by bacterial infections were assigned to the category, "possible antibiotics". Other plants were assigned to the category "tonic".

Ninety nine methanolic extracts of plants traditionally used by first nations were screened against eleven bacterial strains, of which eighty nine demonstrated significant antibiotic activity. Seventy of the extracts showed activity against both Gram negative and Gram positive organisms, and forty six exhibited activity against the antibiotic supersusceptible strain of *P. aeruginosa* Z6l. Fifty one extracts were found to be active against *S. aureus* meth(s) and seventy five against *S. aureus* meth®. All extracts were active against methicillin resistant strains and six extracts active against *K. pneumoniae*.

Extracts with the broadest activity (against at least ten bacteria) were: *Alnus ruba* catkins and bark, leaves of *Fragaria chiloensis, Moneses uniflora* aerial parts, and branches of *Rhus glabra.* In addition, the following extracts were active against nine of the bacteria: branches and roots of *Arctostaphylos uva-ursi,* aerial parts of *Artemisia ludoviciana* var. *latiloba, Balsamorhiza sagittata* aerial parts and roots, *Cornus canadensis* aerial parts, roots of *Geum macrophyllum* and of *Heuchera cylindrica,* branches of *Juniperus communis* and *Larix occidentalis*, roots of *Lomatium dissectum*, and branches of *Ribes sanguineum.*

Secondly, extracts with the greatest activity against normal strains of *P. aeruginosa* K99 were: branches of *Juniperus communis, Ribes sanguineum and Rhus glabra,* aerial parts of *Argentina egedii* and *Cornus canadensis,* leaves of *Fragaria chiloensis,* and rhizomes of *Polystichum munitum.*

Extracts with the greatest activity against the methicillin-resistant strain of *S. aureus* were: *Alnus rubra, Ambrosia chamissonis, Lomatium dissectum, Nuphar lutea* and *Rhus glabra.*
A higher percentage of flowering plants tested exhibited antibiotic activity than did non-flowering plants, but among the latter, the taxa presenting the greatest degree of antibiotic activity were ferns (Filicinae) and conifers (Gymnospermae). The specific results of phase one antibiotic screening by family, species and strains are given in McCutcheon (l996)

Phase I Anti-Fungal Screening

In this phase, a hundred methanolic plant extracts were screened for antifungal activity against nine fungal species. Of these, eighty one had antifungal properties and thirty extracts showed activity against four or more of the assayed fungi. All of the plants traditionally used as antifungal medicines exhibited activity, including all of the gymnnosperms and ferns assayed.

Extracts with the greatest antifungal activity came from: catkins of *Alnus rubra,* aerial parts of *Artemisia ludoviciana, A. tridentata,* and *Moneses uniflora,* and roots of *Geum macrophyllum,* and *Mahonia aquifolium.* Extracts from the following also showed antifungal activity against all nine of the fungi used: *Asarum caudatum, Balsamorhiza sagittata, Empetrum nigrum, Fragaria chiloensis, Glehnia littoralis, Heracleum maximum, Heuchera cylindrica, Ipomopsis aggregata,* and *Rhus glabra.*

The author also found that eighty percent of those plants tested which were traditionally used by first nations had significant antifungal activities, and the analysis of the results by taxa would suggest that more non-flowering plants should be screened in the future for antifungal activity.
In general there is a high correlation between plants with antifungal and antibiotic activity, with several exceptions. Thus extracts of *Arctostaphylos uva ursi, Juniperus communis, Lomatium dissectum, Nuphar lutea* and *Ribes sanguineum* illustrated significant antibiotic activity, but their antifungal properties were poor. Similarly extracts of *Asarum caudatum* and *Ipomopsis aggregata* showed poor antifungal activity but inhibited growth of all nine fungi in the fungal screening.

Phase I Anti-mycobacterial Screening

In this phase a hundred methanolic plant extracts were screened against *Mycobacterium tuberculosis*

and a resistant strain of *Mycobacterium avium*. Thirteen of the nineteen extracts which were found to be active against *M. tuberculosis* were traditionally used by BC first nations to treat tuberculosis. Extracts derived from the roots of *Heracleum maximum,* aerial parts of *Monoses uniflora,* and the inner bark of *Oplopanax horridus* inhibited the growth of both organisms at concentrations equivalent to twenty mg. of dried plant material per disc. Also extracts from bark and catkins of *Alnus rubra,* the branches of *Empertrum nigrum,* and the roots of both *Lomatium dissectum* and *Glehnia littoralis* completely inhibited growth of both organisms at concentrations equivalent to one hundred mg. dried plant material per disc.
With increasing resistance of TB, the treatment has multiplied to a combination of drugs (typically rifampin, plyrazinamide and isoniazid). However starting in the mid-l980s, there has been an increase in cases of multiple drug resistant TB, and many strains are now resistant to seven of the most effective TB drug treatments.

In this phase of screening, six extracts were found to be highly effective in completely inhibiting the growth of both organisms: *Empetrum nigrum, Glehnia littoralis, Heracleum maximum, Lomatium dissectum, Moneses uniflora,* and *Oplopanax horridus.* Three of these extracts are all members of the same family, the Umbelliferae, which is well known for its photo-cytotoxic furano-coumarin components, which may be responsible for observed antimycobacterial activity.

Phase I Antiviral Screening

Screening of the same extracts was conducted against seven viruses for antiviral activity. At non-cytotoxic concentrations, twelve extracts were found to have antiviral activity: extracts of *Rosa nutkana* and *Amelanchier alnifolia* (both Rosaceae) were active against an enteric virus, and a root extract of another Rosaceae, *Potentilla arguta,* completely inhibited a respiratory virus. A branch tip extract from *Sambucus racemosa* was found to be active against respiratory syncytial virus and extracts from the inner bark of *Oplopanax horridus* partially inhibited the same virus. Extracts from *Ipomopsis aggregata* strongly inhibited parainfluenza virus type 3, and a root extract from *Lomatium dissectum* completely inhibited cytopathic effects of rotavirus. Finally extracts from the following plants showed antiviral activity against herpes virus type l: *Cardamine angulata, Conocephalum conicum, Lysichiton americanum, Polypodium glycyrrhiza,* and *Verbascum thapsus.* None of the extracts exhibited broad spectrum effects. Each extract inhibited the growth of only one type of virus.

These results contain antiviral leads, distinct from the current mainstream attempts to create narrow spectrum drugs effective against specific molecular targets. Given the significant portion of extracts which yielded positive results in the antiviral screenings, McCutcheon has concluded that it is reasonable to assume that there are undoubtedly numerous types of antiviral compounds in the source materials. Characterization of active ingredients of the sources is a priority before these plants are lost in BC.

Much of this characterization is on-going. Saxena (l994) has isolated three antibiotic compounds (two new) from *Rhus glabra,* which exhibited the strongest broad-spectrum antibiotic effects of all the extracts screened by McCutcheon, although it showed no activity in the other screens. Similarly *Alnus rubra* had strong antibiotic, antifungal and antimycobacterial effects, and Saxena (l995a) has isolated two active compounds for *A. rubra* bark –oregonin and diarylheptanone.

Matsuura (1995b) has isolated four antibiotic compounds from *Ceanothus velutinus* and four antimycrobial compounds from the same species (l995c). Matsuura (l995d) also has isolated Catechin and an unknown triterpene from *Geum macrophyllum,* and seven active compounds from *Glehnia littoralis*. (l996)

Two of the plants demonstrating strong antifungal activity, *Moneses uniflora and Ipomopsis aggregata*, have also been the subject of chemical investigation, and Saxena (l995b) has isolated a novel chloroquinone (8-chlor-chimaphilin) from *M. uniflora*, in addition to a known antimycrobial compound, chimaphilin. This researcher has also isolated four active compounds from *I. Aggregata,* giliacoumarin, cucubitacin B, resorcinol, and hydroquinone glucoside (l995c).

The efficacy of virtually all the above chemical isolates did not compare favourably with those of commercially-available antibiotics and antivirals. McCutcheon notes that *"the relatively poor activity of all these isolated pure active compounds appears to be at odds with the strong activity exhibited by the crude extracts of the plants they were isolated from. Particularly in the plants with many compounds, synergistic interactions may account for this difference however this possibility has not been explored"*. (emphasis added.) p. 72.

Saxena (l995d) has also isolated a novel antimicrobial compound from *Oplopanax horridus,* which was the most promising extract source in the antimycobacterial assays.

It is interesting to note that three of McCutcheon's antiviral extracts arose from plant species which are members of the Rosaceae (*A. alnifolia, P. arguta,* and *R. nutkana*), and all three of these were active against viruses infecting the mucosal surfaces.

Although the research is far from complete, with the exception of *O. horridus*, none of the above chemical investigations has yet led to the commercial development of anti-infectious compounds. But most traditionally used first nations plants have not been tested, and future screening must take into consideration synergistic effects and continue to employ traditional usage as selection criteria, including both flowering and non-flowering plants and plants traditionally used as tonics, the treatment of bacterial infection, and so forth.

Phase II Screening

In the second part of the screenings, the selection criteria of plants was expanded to traditional use in North America (rather than just BC) although plants were generally gathered in the Pacific Northwest. It was also realized that many medicinal plants prescreened by indigenous peoples have been classified as non-medicinal because the traditional use was not recorded. (This problem can be overcome by excluding in analysis plants from medicinal genera from the category of non-medicinal plants). Secondly the ethnobotanical literature is full of taxonomic misclassifications at the species level because many genera are extremely difficult to identify. However the main criterion of selection of plants remained the traditional use.

In this phase a representative collection of plants medicinally used by first nations of western North

America was collected. The primary focus involved plants used to treat abscesses, burns, infected sores, skin ailments, tuberculosis and yeast infections. In antibiotic screening, clinically important pathogens and multiple drug resistant strains were used.

Most active broad spectrum antibiotics were found in extracts from *Abies grandis, Elliottia pyroliflorus, Geum triflorum, Horkelia fusca, Paxistima myrsinites, Paeonia brownii, Phylloce empetriformis, Picea sitchensis,* and *Pseudotsuga menziesii.*

In addition, the following plant extracts showed extremely strong activity against at least one organism: *Ephedra nevadensis, Arctostaphylos patula, Epilobium angustifolium, Mitella breweri, Oenothera villosa,* and *Potentilla norwegica.*

At the family level, the Ericaceae, the Polypodiaceae and the Rosaceae showed comprehensive antibiotic activity. (Chimaphilin and arbutin, commonly-known antibiotic compounds, are constituents of the Ericaceae; however, there is little work to date on the Rosaceae and the Polypodiaceae, and antibiotic constituents are unknown). The author also has found that among the non-flowering plants, there was a striking difference between percentage of active extracts from the Filicinae and Gymnospermae (l00%) and lower plants (54%).

In phase II antifungal screening, the most active broad spectrum antifungal extracts arose from: *Boykinia occidentalis, Chimaphila umbellata, Drosera rotundifolia, Epilobium angustifolium, Geum triflorum, Horkelia fusca, Oenothera villosa, Paeonia brownii, Potentilla norwegica, Trillium ovatum,* and *Woodsia scopulina.*

Three plant families were extraordinary in the anti-fungal screening: Pinaceae, Rosaceae, and Saxifragaceae. All samples from these families showed antifungal activity.

This second phase of screening also focused on *Artemisia* species, perhaps the most important medicine source of North American first nations, and until this study, few North American species had been screened. Seventy four samples from thirty *Artemesia* taxa were screened for antibiotic activity. All samples showed activity against at least six bacteria, except *A. absinthium.* The strongest activity was demonstrated by *A. frigida, A. ludoviciana, A. tridentata, A. dracuncullus, A. tridentata. A. douglasiana, A. cana, A. spiciformis,* and *A. tridentata.* These are also the species mentioned most frequently in the ethnobotanical literature. It was also found that constituents of plant materials were most potent just before flowering

Seventy four extracts prepared from thirty *Artemisia* species were assayed also for antifungal activity against eight fungi. Antifungal activity was found to be distributed throughout all four subgenera, and the strongest and broadest spectrum of activity was demonstrated by *A. douglasiana, A. fridiga, A. dracunculus,* and *A. tridentata,* (again the species most frequently cited in ethnobotanical literature). Some of the therapeutic effects of these species were found to be light enhanced.

Finally seventy five extracts from thirty one *Artemisia* taxa were screened for antimycobacterial activity against *Mycobacterium tuberculosis* and *M. avium*. Extracts with the greatest antimycobacterial activity arose from *A. dracunculus, A. cana, A. nova, A. tridentata,* and *A. tripartita.*

Seventy three extracts were screened also against eleven viruses: Sindbis, polio one, Coxsackie and murine cytomegalovirus plus other viruses. Four extracts inhibited cytopathic effects of Coxsackie and polio virus. Eight extracts (from the Tridentatae, Vulgares and Absinthium) partially inhibited respiratory syncytial virus; Five extracts (from Vulgares and Tridentatae) partially inhibited corona virus, and none of the *Artemisia* extracts inhibited herpes virus, parainfluenza virus, rotavirus, vaccinia virus and vesicular stomatis virus. Although wide spectrum screening showed that antiviral components of *Artemisia* species are widely distributed throughout the genus, activity was not consistently shown by samples from the same taxa, and this variation was thought to result from both qualitative and quantitative differences in the chemical composition of the species during the growing season.

The results of the above screenings show that *Artemisia* species exert significant anti-infectious activity *in vitro* against viruses, fungi and bacteria, and these species are good candidates for further investigation. Secondary metabolites of *Artemisia* species have been widely investigated, and Marco (l990) has reviewed the 376 constituents reported up to l988. These generally belong to four major classes: coumarins, flavonoids, terpenes and acetylenes.

One must, of course, be cautious in extrapolating *in vitro* studies such as that of McCutcheon's antibacterial/fungal/viral screenings to human models. The anti-bacterial activity of *Fragaria chiloensis*, for example, is possibly a result of its tannic constituents. The work in this thesis just scratches the surface of BC first nations medicinal plants, and beyond antifungal, antibiotic, anti-*Mycobacterium* and antiviral assays, most other pharmacological activity and effects of first nations plants has yet to be clinically assessed.

New Product Source II --Wood "Waste"

In addition to the plant species identified from first nations use as reasonable sources of medicines, biocides and nutraceuticals, the barks of three species, lodgepole pine (*Pinus contorta),* Sitka spruce (*Picea engelmanni x glauca*) and alder are known to contain phenolic (anti-oxidant) compounds, which could be sold into the nutraceutical markets if they can be extracted at commercially-viable rates. This makes a lot more economic sense than burning the bark, as is now the case. In fact many other tree species have traditionally provided medicines from their bark including Grand Fir, Western Hemlock, Douglas fir, as have shrub species such as Birch, Arbutus, Bitter cherry and Aspen.

As part of normal processing in the BC forest industry, logs are debarked and together with other wood "waste" which cannot be made into pulp are dumped into a fuel pile which is used to heat boilers of BC pulp mills. In saw mills this waste is burned in beehive burners, which are being phased out for environmental reasons. BC mills will then be faced with the problem of disposing of hundreds of millions of pounds of waste bark annually. This bark can be used as a continuing source of bioactive chemicals and further isolation and characterization of various species' barks for organic compounds should be undertaken for antifungal, antibacterial and insecticidal properties. There is a real potential to exploit forest-based, naturally occurring insecticidal compounds within the forest industry itself –for the control of economically-significant forest pests and in the production of seedlings used in reforestation. (The biocidal properties of forest substances are taken up in a subsequent section).

New Product Source III --Soil Microfungi and Lichens

Another area of focus for new products should be soil microfungi and bacteria, less than 0.1 percent of which have been screened for medicinally useful compounds in BC. It is difficult to screen such compounds since the normal ways of isolating them requires that significant quantities of microbes be grown in the laboratory. This is arduous and often soil microorganisms refuse to reproduce outside of their natural conditions. TerraGen has circumvented this problem through taking a soil sample, which typically contains 5,000 species of microorganims, extracting all the DNA from it and inserting pieces of the DNA into *Streptomyces* bacteria.

Since the bacteria then contain genes of differing microorganisms, they produce some of the chemicals usually found only in the original soil organisms. Using these techniques TerraGen has isolated potential new antibiotics from BC soil samples and is using the same techniques on lichens (a symbiotic linking of fungi and algae). Roughly 20% of the earth's fungi grow in such symbiotic relations and may contain a diversity of medical chemicals, but lichens cannot be grown in the laboratory. Lichens actually contain two or more organisms—a fungus and an alga or a cyanobacterium, or both. Since the component organisms engage in complex intracellular signaling, lichens have the potential to yield a variety of biochemicals with pharmaceutical utility.

New Product Source IV. – Canopy Arthropods and Insects

Another potential source of new pharmaceuticals and pesticides are poisons and exudates of arboreal arthropod and insect species associated with montane old growth forests. Recent field work on canopy insects, for example, in the Carmanah Valley (C. French personal communication) show that multiple species, many of which are entirely new to science, live in the canopies of coastal old-growth forest and perform basic roles in ecosystem functions. For evident reasons, the poisons exuded by creatures such as spiders and snakes have an extensive folk history of medicinal use throughout many cultures.

To give a single modern example, in mid-l998, a team from the University of Southern California led by F. Markland, announced that a protein in the venom of copperhead snakes called contortrostatin dramatically retards the growth of breast tumours and can inhibit the growth of other forms of cancer. (Vancouver Sun, August 27, l998). In studies with mice implanted with human breast cancer cells, there was a 60%-70% reduction in growth rate of breast tumours and a 90% reduction of tumours which had spread to the lungs. The team is genetically engineering the venom, which apparently inhibits angiogenesis –the development of new blood vessels exploited by tumour sites to get nutrients and as a pathway to spread. The protein from the copperhead inhibits the formation of new blood vessels to nourish tumours and thus helps prevent metastasis. This protein belongs to a class called disintegrins (because they disrupt the functioning of other proteins on the cell surface).

In this context, L. Humble and a team from the Canadian Forest Service (Humble l997) are investigating the effects on canopy arthropods of alternative silviculture systems and specifically are trying to answer this question: what habitat attributes are necessary to maintain natural populations of canopy dwelling insects and other arthropods in coastal montane forests? In other research, G. Scudder of UBC's Department of Zoology is producing a handbook for the identification of BC's plant bugs (Hemiptera:Miridae). Western forests are dominated by the arthropods, which constitute over 87% of all forest faunal species. And yet their study is often ignored in favour of the forest-floor dwelling carabid beetles.

VI. BC Medicinal Herb Wildcrafting

Introduction

In addition to the part of the pharmaceutical sector in BC which is involved with natural products, there is also a sector called "wildcrafting" which gathers medicinal and nutraceutical species from wildlands and sells generally to US herbal companies in bulk form.

BC forests and wildlands, we have seen, contain a wide diversity of plants with market potential for the manufacture of pharmaceutical compounds and herbal medicines in addition to nutraceuticals. (The markets for forest plants used as natural food preservatives are also expected to grow).

Many of the medicinal and nutraceutical plants are easily grown in small crops and thus are not appropriate candidates for forest gathering. In l998 the main medicinal herbs which are grown in North America are: Echinacea, Goldenseal, Ginko, St. John's Wort, Hops, Peppermint, Slippery Elm, Aloe, Saw Palmetto and Valerian. Goldenseal, St. John's Wort, Echinacea and Slippery Elm are also wildcrafted, and Saw Palmetto is both cultivated and wildcrafted, mainly for export to Europe to be incorporated into phytomedicines. But some of these such as St. John's Wort are currently in such demand that buyers are grateful to get them from anywhere.

Many others botanicals are appropriate candidates for wildcrafting and those currently being taken from the Chilliwack forest district include: serviceberry, liverwort, Valley Cinquefoil, Red Elderberry, Pearly Everlasting, BitterCrest, Scarlet Giblet, skunk cabbage, wild rose, Mullein, spruce bark, and Devil's Club (an estimated 2,500 lbs. from this district alone during l997).In addition *Apocynum androsaemifolium, Arctostaphylos uva ursi, Asarum spp. Chimaphila spp. Ganoderma spp., Formitopsis pinicola, Mahonia spp. Populus tremuloides, Solidago canadensis,* and *Thuja plicata* were also taken.

Little yew is being collected in BC because there is now a commercially feasible semi-synthetic taxol approved for drug use in the US and Canada. The semi-synthetic procedure for the production of taxol still depends on harvesting the plant because it uses a taxol precursor found in *Taxus* species. In other words, now the bark from the pacific yew is no longer the only source of taxol (as it was until around l994), and other T*axus* species besides *T. brevifolia* can now contribute to the production of taxol. For example, the starting compound in this partial synthesis, l0-DAB, is easier than taxol to extract, and occurs in considerably higher concentrations (10 times) in other yew species such as *T. baccata*.

Although at the present time, l0-DAB can be obtained only from *Taxus spp*., it is present in all components of the species (not merely the bark), and can be obtained from a wide variety of widely planted shrubs, This is the basis of Weyerhaeuser Co's large plantations in the US which grow millions of three year old yew trees derived from cuttings of rapidly-growing horticultural yew varieties, and after five years extract taxol and other taxanes. The millions of tonnes of discarded yew needles and twigs harvested yearly by commercial growers are also now contributing to the supply of l0-DAB (Ellis and Russin undated).

For all of the above reasons, the collecting of pacific yew bark and other parts has almost stopped in BC. The evolution of yew gathering – extensive in the early nineties and slacking off now illustrates another point about medicinal plants. Interest is first kindled in traditionally used medicinal plants, and an effort is made to extract active ingredients and synthesize these or partially synthesize them (starting with a precursor as in the case of taxol). It is often very difficult to commercially synthesize or partially synthesize such substances –the vast majority of organic molecules which nature throws forth cannot be cheaply synthesized – And yet such syntheses do occur, and in that case there is no longer a reason (from the viewpoint of pharmaceutical companies) to pay wildcrafters for plant parts gathered from the forest. The latter business (selling raw substances to the pharmaceutical companies) is suddenly over. And yet if the therapeutics of forest botanicals in some cases, arise from a synergistic interaction of different organic compounds, as an increasing number of consumers believe, there are still may be growing market opportunities to sell the original plant into the herbal markets even after and "active ingredient" has been synthesized. Such was not the case with yew because so little taxol is present in bark and the chemical synthesis is far too expensive. The current main seller of pacitaxel, BMS, gets much of their yew from thousands of gardeners trimming hedges in Britain.

Medicinal Wildcrafting Industry Structure

When one is looking for export values or volumes of BC medicinal plants taken from the wild, (or grown), Statistics Canada data is less than helpful. Starting in l988, Statistics Canada and other government agencies aggregated import and export figures in terms of the "Harmonized Commodity Code". Medicinal botanicals fall under HCC l2ll.00 – "Plants and parts of plants ….used primarily in perfumery, in pharmacy or for insecticidal , fungal or similar purposes, fresh or dried". This category is, somewhat eccentrically, broken down into HCCl2ll.l0 - liquorice root, HCC1211.20 - Ginseng root, and HCCl2ll.90 -Not elsewhere specified.

First it is impossible to separate volume and value figures for medicinal botanicals from those for perfumes and insecticides. Also the kg. volume figures do not reflect whether the item was fresh or dried (a ratio variation of 4-l5:l). And it is precisely "Not elsewhere specified" (everything besides liquorice root and ginseng) that we wish specified; that is, volume and value of exports by species.

There is the additional problem that any exporter dealing with Canada Customs will do everything in her power to get the export classified as a food or food supplement rather than a medicine to save time and money. Therefore the Statistics Canada export figures for HCCl2ll.90 –which for l997 was l08,345 kg. with a value of $l,028,000 –involve significant under-estimations.
Parenthetically, in order to track the export figures on these growing resources, the provincial government should lobby Statistics Canada to include more specificity in this data – at least to separate

medicinal, perfume and insecticidal plant data and to aggregate in terms of the main herbal species growing into prominence on the US market.

Given the above problems, to obtain the following, we therefore sought information directly from commercial harvesters of medicinal plants in BC, Oregon and Washington. Commercial wildcrafters were asked these questions: What do you collect? How much of each in a good and bad year? How much do you receive per pound? What are your expenses and profit margin by pound by species? How do you pay pickers? What are your gross revenues in good and bad years? To whom do you sell?

The gathering of forest medicinals, both commercial and otherwise, in BC is centered mainly in the Kootenays, the Slocan region and the Okanagan (St. John's Wort taken off of range land). Excluding hobby gatherers from urban areas who go out on weekends, there were an estimated 300 persons gathering commercially in BC during l997 (half of these in the Kootenays) and these numbers include an estimated l5-20 serious commercial collectors, who operate either through a company or through their own name, hire crews, and methodically gather. The serious commercial collectors of wild medicinal herbs sell almost exclusively to US bulk nutrient suppliers and big manufacturers such as Frontier. In excess of 95% of both value and weight of the wildcrafted medicinal herbs in BC during l997 were accounted for by St. John's Wort and Oregon Grape.

Often serious wildcrafting efforts have been an extension of businesses which farm organic alternative crops and several of these produce St. John's Wort extract and have products manufactured on contract (such as Freshwoods Farms).

Estimated l997 gross revenues paid to the l5-20 commercial collectors were between Can. $2 - $3 million. Crews who work for these collectors are generally paid on a per pound basis (in the range of $.50-.70/lb) and can make around $l00.00 daily.

The main medicinal botanicals gathered in BC during l997 (both in terms of revenues generated and weight) were Saint John's Wort and Oregon Grape, followed by cedar oil. Medicinal botanicals wildcrafted in smaller quantities in BC during l997 included Devil's Club, Nettles, Burdock, Yarrow, Mullein, Arnica, Camomile, Tansy, Rose Hips, Cascara, Desert Parsley, Yew, lichens such as *Usnea wirthii*, and many other species.

The gathering of wild medicinal plants is really a craft industry in BC and is usually not yet organized into companies. People generally gather for their own use, and some small sales in the community of dried raw plant materials or extractions.

During l997 we estimate that between l00,000 and l50,000 lbs (dry yield) of Saint John's Wort were wildcrafted in BC, 20,000 lbs of dry Oregon Grape, 6,000 lbs of cedar oil (made mainly from boughs) and less than 5,000 lbs of Devil's Club bark. It was not possible to make reliable estimates of the quantities of other medicinal botanicals harvested from the wild in BC.

Wildcrafted Harvest of Medicinal Botanicals in the Pacific Northwest

Three years ago, before the market took off, approximately 10,000 lbs (dry) of Saint John's Wort were harvested from the wild in BC and Washington state together. Last year, approximately 400,000 lbs of Saint John's Wort were wildcrafted in Washington state, approximately 200,000 lbs in Oregon and, as noted, around 100,000-l50,000 lbs in BC. The dry wildcrafted harvest of Saint John's Wort this year in BC may exceed 300,000 lbs if it can be harvested before being burned up by the unusually hot weather and interior fires during July and August of l998.

With respect to Oregon Grape, three years ago, the Washington State wildcrafted harvest was approximately 4,000 lbs, with an equivalent figure for BC. In l997 the wildcrafted harvest for Oregon Grape in Oregon was around 20,000 lbs with the Washington harvest about half of this, and a BC l997 harvest of approximately 20,000 lbs.

In terms of weight and revenues, the third main medicinal botanical crop of the Pacific Northwest in l997 was Cascara Segrada. In l997, approximately 400,000 lbs of Cascara were wildcrafted in Washington state, and around l20,000 lbs in Oregon. It was not possible to make a reliable estimate of the amount of Cascara Segrada harvested from BC during l997.

July l998 Prices Paid to Wildcrafters

In July l998 St. John's Wort with a 0.l5% hypericin content received around US $4.00-US $5.00 /lb. from brokers, with dry Oregon Grape fetching in the neighbourhood of US $l.40-$l.80/lb and Cascara Segrada around US $l.40/lb-$3.50/lb. These are the amounts which wildcrafter companies are paid through brokers and other buyers. Generally the range of prices for a specific species depends on market demand and availability, potency, amounts sold, whether or not the product is organic and plant part sold (flowers as opposed to stem bark, for example). Reputable buyers purchasing from wildcrafters will be concerned where a botanical was picked to ensure that it does not contain roadside herbicides. In general wildcrafters can make more money by selling their crop into the herbal products industries rather than selling to pharmaceutical companies. Quality dried yarrow, for example, fetches around Can. $l0.00 per pound in the former markets and only Can. $4.00-5.00 per pound from pharmaceutical manufacturers.

St. John's Wort costs on average around $2.00/lb to pick and transport and around $2.00/lb for primary processing (drying and bagging). If wildcrafter companies receive only around $5.00/lb (the current price), their profit margins are so low that their cash outlays to pickers restricts the amounts that can be picked, unless they find a buyer who is willing to front half of the cash . There is also a current restriction on the total upper tonnage of St. John's Wort which can be wildcrafted in BC due to limited drying facilities, with several firms using the facilities of Ginseng growers during July through September.

Prices can also change suddenly when large, new entrants grow a botanical. In the early nineties, growers and wildcrafters were paid a high price for Evening Primrose Oil, which was supposed to be the salvation of tobacco farmers in Ontario. (David Sim, personal communication). Unfortunately in l992 the government of China suddenly allowed farmers to sell non-staples for foreign currency, the Chinese flooded the Evening Primrose market and five years later, when the Chinese finally cleared their grown stock, prices had fallen to less than a third of the l993 price.

Market Opportunities for Wildcrafting Medicinals and Nutraceuticals

The growing interest in plant-based remedies and nutraceuticals is creating new market opportunities for wildcrafting, agroforestry and growers. But we know very little about these commercially valuable species growing in BC. Take St. John's Wort. The North American market for this species exploded in l997 and price depends on hypericin content. We do not know: how much of this grows wild in BC and where; or when it should be harvested to maximize hypericin content. If wildcrafting companies had this basic knowledge, they could more optimally maximize hypericin content and up their asking prices. Similar observations are applicable to the other species such as Devil's Club, Oregon Grape and all those listed in Figure 8.

An argument can be made for mainly growing these botanicals as crops rather than gathering from the wild. These matters are taken up in Part II.

The European market for medicinal botanicals is around five times the size that of the US plus Canada, and the European market for items such as the laxative made from *Cascara segrada* bark is almost twenty times that of the US. Even so, *Cascara segrada* is an ingredient of in excess of two hundred products sold in Canada including Cascara Segrada Tab 200mg (Parke Davis), Aromatic Cascara Fluid Extract (Shoppers' Drug Mart), Laxatif aux Herbages Tab (Bioforce Canada Ltee.), and Sachet pour Infusion Laxative (Frega Inc.). Also several veterinary products contain this substance: Purgex Inj. (Fatro Inc., Canada), Laxative Injectable (Veterinary Labs Inc) and Laxative Inj. 20% (Armitage Carroll Ltd.). (Prescott-Allen and Prescott-Allen, l994). Other widely employed plant substances in Canada are St. John's Wort and uva ursi from *Arctostaphylos uva-ursi*—an active ingredient of in excess of l50 products sold in Canada.

Figure 9 presents some common BC medicinal botanicals which are amenable to wildcrafting plus their current l998 wholesale price/lb. In general wildcrafters are paid approximately half to one quarter of this wholesale price., although in the case of expensive items such as inner stem bark of *O. horridus* or those especially difficult to gather, they may be paid up to two thirds of the wholesale price. Prices were gleaned and averaged from Canadian and US bulk herbal suppliers and brokers. Clearly the short term "best economic bets" for wildcrafting medicinals in BC are St. John's Wort, Oregon Grape and Devil's Club. Some of these prices are high-end wholesale prices for organic produce and were included to show the amounts which these species can fetch. There is also sometimes a considerable price variation depending on part source. Cedar oil from chips is currently selling for around Can. $30/lb, but when extracted from boughs it can bring between Can. $8.00/lb and Can. $60.00/lb.

Figure 9 -- Selected BC Indigenous Medicinal Plants for Wildcrafting and Sales into the North American and European Markets, and July l998 Wholesale Prices

Name	**Wholesale Price ($Can/lb.), dried**
Alder bark (*Alnus rubra)*	$ 3.00-$5.00
Alum root (*Heuchera ylindrica)*	$12.45
Avens *(Geum macrophyllum)*	$12.00
Arnica (*Arnica latifolia)*	$ 9.95
Baneberry *(Actea rubra)*	$12.00
Bittercherry bark (*Prunus marginata)*	$18.00
Bittersweet (*Solanum dulcamara)*	$12.00
Bleeding Heart root (*Dicentra formosa)*	$11.00
Bloodroot (*Sanguisorba canadens)*	$39.95
Burdock (*Arctium minus)*	$ 7.45-$14.30
Bunchberry (*Cornus canadensis)*	$12.00
Cattail pollen (*Typha latifolia)*	$80.00
Cascara segrada (*Mentha citrata)*	$11.95
Cedar Oil (*Thuja plicata*)	$8.00-$60.00
Chickweed (*Stellaria media*)	$ 8.75
Chokecherry (*Prunus virginiana)*	$23.00
Club Moss *(Lycopodium clavatum)*	$10.95
Colt's Foot (*Petasites palmatus)*	$26.00
Dandelion (*Taraxacum officinale)*	$6.00-$10.00
Devil's Club (*Oplopanax horridus*)	$30.00-$85.00
Dogbane root (*Apocynum andraesimifolium)*	$31.50
Elder flowers (*Sambucus caerulea)*	$11.60
Feverfew *(Tanacetum parthenium)*	$18.75
Fireweed root (*Epilobium angustifolium)*	$22.00
Giant Horsetail (*Equisetum telmateia)*	$18.00
Goldenrod *(Solidago canadensis)*	$ 7.95
Hawthorn leaves (*Crataegus douglasii)*	$ 6.65
Heal all (*Prunella vulgaris)*	$ 9.95
Horsetail (*Equisetum hyemale)*	$ 7.10
Indian Hemp *(Apocynum cannibinum)*	$10.00
Kinnikinnik (*Arctostaphylos uva ursi)*	$ 5.50
Lady Slipper root *(Cypripedium montanum)*	$82.95
Licorice Fern (*Polypodium glycyrrhiza)*	$14.00
Madrone (*Arbutus menziesii) leaf*	$10.00
Male Fern (*Dryopteris felix-mas*)	$10.10
Mullein (*Verbascum thapsus)*	$ 8.00
Nettle Leaf, organic (*Urtica dioica)*	$13.75
Oakmoss *(Evernia prunastri)*	$ 5.75
Oregon Grape root *(Mahonia aquafolium)*	$4.00-$l4.50
Pearly Everlasting (*Anaphalis margaritacea)*	$13.75
Pipsissewa (*Chimaphilia umbellata)*	$10.00

Name	Wholesale Price ($Can/lb.), dried
Pleurisy Root *(Asclepius speciosa)*	$l4.66
Rasberry Leaf *(Rubus idaeus)*	$ 4.95--$14.95
Reed Root (*Ceanothus velutinus)*	$16.00
Scullcap (*Scutellaria galericulata)*	$20.00
Sheep Sorrel *(Rumex acetosella)*	$7.45
St. John's Wort *(Hypericum formosum)*	$ 8.55
Strawberry Leaf (*Fragaria vesca)*	$ 7.95
Tansy *(Tanacetum vulgare)*	$ 6.95
Valerian (*Valerian sitchensis)*	$6.65-$18.50
Willow flowers (*Salix sp*)	$19.22
Yarrow (*Achillia millefolium)*	$ 6.55

This species of St. John's Wort, in addition to being an anti-depressive, also contains two compounds which strongly inhibit a variety of retroviruses (Neil Towers personal communication). Burdock is still classified by the BC Ministry of Agriculture as a noxious weed, and (the very invasive) St. John's Wort contained with biocontrol agents. (To the extent possible, biocontrol of St. John's Wort should be immediately replaced with wildcrafter agreements).

In addition to Devil's Club, Cascara bark, St. John's Wort, and Black Hawthorne, (*Crataaegus douglasii*), Ladyslipper, which is a threatened orchid taking fifteen years to grow, hemp dogbane (A*pocynum cannabinum*), *Valerian sitchensis*, *Circaea alpina* (nightshade) and *Equisetum pratense* (horsetail) are all indigenous BC plants which are much in demand on the European herbal markets now. Premium prices are paid for produce which is organically grown or wildcrafted. Other "hot" botanicals showing rapid market growth include Black and Blue Cohosh, (threatened and growing in eastern Canada but not BC), Blood Root, and alder bark for its anti-oxidant compounds.

In the US medicinal plants for the complementary medicine and herbal supplement consumer are sometimes marketed mainly through regional botanical purchasing houses which process and package plant parts for either final processors or the retail market. The standard methods of purchase involves either spot buying or a contract in which the wildcrafter ships on a monthly basis, and large (5,000lb) buyers often offer processing as part of their service to end product manufacturers (De Geus l995). But increasingly, growers and wildcrafters are selling directly to end product manufacturers who are having difficulty getting certain botanicals in bulk. The large manufacturers prefer to purchase 5,000-to-l0,000lb quantities monthly or bi-monthly. It is worthwhile to note here that in Viten's (l998) study of the BC nutraceutical manufacturers, Canadian companies purchased raw materials almost exclusively from growers rather than wildcrafters, who generally sold to US concerns. The BC medicinal/nutraceutical herb growers, in turn, sell about three quarters of their produce by weight to BC concerns and the remainder into the US (A. Gunnar personal communication).

l997 Top Selling Herbal Supplements in US Mass Market

Figure 10 presents the l997 US mass market sales of the top herbal supplements for the l2 week period ending l2/28/97 and 52 week period ending the same date. Total l997 sales were US $44l,502,560.

Figure 10 -- Top Herb Supplement Sales in the US - 1997

Total Sales (US$)	l2 Week Period	52 Week Period
Total Supplements	$141,227,680	$441,502,560
Ginkgo	29,425,772	90,197,288
Ginseng	20,057,994	86,048,080
Garlic	17,870,164	71,474,288
Echinacea/Goldenseal	19,114,476	49,189,576
St. John's Wort	28,081,530	47,774,79 2
Saw Palmetto	5,789,359	18,381,592
Oregon Grape	2,479,788	9,965,772
Evening Primrose	1,789,713	7,299,353
Cranberry	1,739,309	6,182,210
Valerian	1,763,096	6,104,450
Bilberry	1,296,568	4,555,723
Milk Thistle	923,081	3,037,672
Kava Kava	933,l82	2,950,132

Source: IRI Scanner Data, FDM

North American Market Trends

Kava based products went from almost nothing in l996 to US $3 million in a single year, and the entire North American nutraceutical market has risen, on average, l4% annually over the last three years. Kava is suddenly competing with St. John's Wort ($47.8 million sales in l997), for the herbal anti-depressant market, since it induces a state of relaxation without fogging the mind, is a strong muscle relaxant, and acts in the same way as prescription anti-stress drugs on neural receptors. In July l998 national television advertisements began on CNN for kava-based formulae, and Kava based formulae plus singles sales have exceeded US $22 million in the first three months of l998.

Public and manufacturers' awareness of research results to some extent drive sales and there have been few research papers on Kava to date. (There are now 38 double blind, placebo-controlled studies on St. John’s Wort) but NIMH has funded two projects on the effects of Kava and recent studies are emerging weekly.

Weather is a big factor for both growers and wildcrafters. For example, St. John’s Wort grown in l996 had a very high hypericin content of around 0.3-0.4 percent, but l997 production, due largely to El Nino conditions has less than a third of hypericin content. Prices for both this herb and for Saw Palmetto (which rose from around US$l.45/lb to about $7.00/lb by the end of the year) were up, quality was down and throughout the year and into l998, US demand has continued to outpace supply.

In addition, many traditionally cheap, easily available herbs such as Goldenseal, Cascara, Juniper Berry, and European Valerian are now scarce and expensive in l998.

At the same time, herbal-based nutraceuticals are becoming a growing category. According to SPIN Distributor Information, both herbal formulae (items containing more than one type of herb) and herbal singles showed considerable growth during the first six months of l997 vrs. the equivalent period in l996. The formulae sales increased by l9.3 percent and singles showed a 77 percentage increase in the same period.

Cold and flu/immune boosting products (such as Echinacea, Goldenseal, Pau d’Arco and Astragalus formulae and singles) showed 25 percent growth in dollar volume during the first six months of l997 vrs. the equivalent period in l996, and other segments presenting consistent growth for the same period comparisons include “calmatives” such as St. John’s Wort, Kava Kava, Camomile, Valerian and Scullcap, (47 percent growth as formulae) and brain/circulation products such as Ginkgo and Gotu Kola, (48.5 percentage increase in dollar sales as formulae).(*HerbalGram* l998.)

Other emerging product categories involve children’s herbal formulae and phytoestrogens. In total, herbal products packaged and promoted for children showed l00 percent increases in dollar sales during the first six months of l997 vrs the equivalent period in l996, and herbal treatments of menopause and menstrual related problems are expected to show rapid growth. Worldwide there is research underway to produce botanical products which can supply naturally occurring estrogens which hopefully will be a more benign alternative to current hormone replacement therapies which may increase the chances of breast cancer. Soy protein is a widely-consumed “estrogen-response modifier”, meant to stabilize a woman’s dwindling estrogen supply, and along with black cohosh root is used to combat hot flashes. Mexican yam, to give a final example, is now a widely-consumed source of diosgenin (New York Times, June 21, l998).

The significant increase in sales of St. John’s Wort reflects a May 5 *Newsweek* article and the June 27 “20-20” TV program which examined this herb as a depression treatment. For many years the total US market for this herb was in the range of 20-60 tons per year. After this publicity demand has increased in the first quarter of l998 to several hundred thousand tons in the US alone. The same thing could happen at any time with several indigenous species from BC, one possible candidate being Devil’s Club.

Although we have not been able to find any reliable estimates of the total tonnage of Devil's Club growing here, it is almost everywhere in BC in profusion. (But so was Goldenseal in North America at one recent time). Devil's Club has virtually all the product characteristics to take off – It has proven anti-fungal, anti-bacterial, anti-viral and anti-myobacterium effects. It has first nations credentials. Together with *Artemisia* species it is one of the most significant spiritual and medicinal plants of Pacific Northwest peoples and was universally used by them. And it is a member of the same family as ginseng and will eventually be used in formulae as a ginseng substitute.

VII. BC Nutraceutical and Medicinal Herb Products Manufacturers

Industry Structure

The third component of the BC medicinal botanical industry involves the manufacturers of nutraceuticals (vitamins, minerals and herbal supplements). We were able to interview fifteen of these companies. In addition, Vitens (l998) has estimated that sales of herbal products to BC consumers were in the range of Can.$44-46 million during l997. As part of her overview, Vitens obtained information on 3l of BC's 50 manufacturers of dietary supplements and medicinal herbs and thus her work profiles around 65% of the industry in terms of companies and around 90% in terms of annual sales. The following discussion is based on both set of interviews.

She found that these manufacturers are engaged in extraction, drying and grinding, encapsulation and packaging, but that only 5 of the 28 reporting companies were equipped to undertake tableting and l0 equipped for encapsulation. Most of these companies lack the technology and facilities for high quality, standardized production.

Sales

With respect to sales, total l996/97 revenues of 25 reporting companies was $l33.55 million, with approximately Can. $55 million arising from the manufacture of herbal preparations and dietary supplements. Since her responding sample represents around 85% - 90% of all BC industry sales, adjusted l996/97 revenues were probably between $l48-l57 million, with sales of manufactured herbal preparations and dietary supplements exceeding $60 million. The average annual growth rate of these companies we have interviewed is 18 percent over the last two years.

With respect to size, the reporting companies employ 1,7l0 persons, with 43 percent employing between l0 and 50 persons, and 27 percent employing between 51 and 200 persons.

Products and Sources of Ingredients

Products ranged from vitamins, minerals and enzymes, shark oil and cartilage to specialty supplements of glucosamine sulfate, and herbal formulae containing Echinacea, Devil's Club and Devil's Claw, St. John's Wort, Valerian, Saw Palmetto, Evening Primrose, Gingko, garlic, Oregon Grape, Feverfew, Black Cohosh, Dong Quai, Wild Yam, Passion Flower, nettles, Saw Palmetto, bilberry, dandelion, pine and cedar bark, borage and flax oil, and Ayurvedic adaptogens. There were no producers who included indigenous medicinal or nutraceutical mushrooms in their formulae.

Excluding species common in the European pharmacoepia such as St. John's Wort and Valerian, the most prevalent BC indigenous botanical being introduced by these companies into herbal formulae during l997 was Devil's Club.

With respect to sourcing and purchasing requirements, most manufacturers sourced from growers rather than wildcrafters (less than 0.l percent of all sourced herbs), and the main requirements for purchase involved correct drying and species identification, colour, texture, odour and taste, and sometimes certificates of analysis which indicate strength of active ingredients, in addition to completed testing for contaminants.

Vitens found that fifteen manufacturers bought medicinal herbs from BC growers, including North American ginseng, Echinacea, St. John's Wort, Valerian, Astragalus, Feverfew, Mullein, dandelion and smaller quantities of other herbs such as Devil's Club.

Sales Areas

These herbal supplement products are sold mainly in BC and other Canadian provinces, although 75 percent of responding firms exported to the US and 42 percent to Asia. In one case a two product line company is selling Devil's Club to distributors in Taiwan. Only eight percent of the responding population reported sales to Europe.

In her survey Vitens asked about perceived advantages and disadvantages in sourcing medicinal herbs from BC. Advantages included freight savings, favourable "made in BC" image and close personal contacts with suppliers. Disadvantages included low supply volumes by growers, higher prices and poor quality.

Sales channels included (mainly) health food stores and pharmacies, followed by vitamin stores and supermarkets. Many manufacturers are also selling directly to consumers now on the internet.

Botanicals Desired in the Future

Finally Vitens asked manufacturers what medicinal plants they would be interested in sourcing from BC growers and wildcrafters n the future: These included the "big three" - Echinacea (*augustafolia* and *purpurea),* St. John's Wort and North American ginseng, plus Goldenseal, Gingko, Borage, Spearmint and Peppermint Other herbs mentioned included: Astragalus, Black and Blue Cohosh, Cascara segrada, *Bidens pilosa,* Devil's Club, Grape Seed, Parsley, Sage, Turkey Rhubarb, Ladyslipper, Black Walnut, Feverfew, Damiana and Iceland Moss.

Production Technology -HPLC

Big bulk buyers like Frontier in the US demand a certificate of analysis to be submitted with samples, even with wildcrafted samples, although many buyers will accept wildcrafted materials without the certificate and just perform their own analysis on samples. Although most BC herbal products manufacturers are deeply concerned with product quality and accuracy of standardization claims, others will sell practically anything, and we have encountered several instances in which concentration levels of ingredients did not match the claims on the label or in which a different species from that claimed was sold.

High performance liquid chromatography (HPLC), we have seen, is the most efficient way to determine the levels of specific required chemicals in bulk material, so the product manufacturer can concentrate active ingredients for the most optimal levels of human consumption. Extensive research in phytomedicine, especially in Europe, has established standards for botanical extracts. Holm and MacGregor (l998) give these examples. Wildcrafted valerian root usually contains low percentages of valerinic acid, while milk thistle usually contains high levels of silymarin. Studies have shown that the optimally effective varierian extracts contain 0.8 percent valerinic acid while extracts of milk thistle have been standardized at around 80 percent because this was found to be the most effective level. In another example, kava is standardized to contain 75 mg. of kavalactones. The pills come in varying strength, from l00 to 250 mg, and the amount of kavalactones also varies. For example, a 250 mg. pill of 30% extract will contain 75 mg. of kavalactones, which is in accordance with Kommission E's recommendation of 60 to l20 mgs daily of kavalactones for stress and anxiety.

Herbalists and physicians who believe that therapeutic effects of herbal preparations arise from a synergistic blend of many organochemicals oppose standardization on a single "active ingredient", but standardization and near pharmaceutical-grade production methods will soon become more prevalent throughout the industry.

There are 6 BC companies, previously mentioned in the discussion on medicinal mushrooms, which can provide a certificate of analysis, test for contaminants such as microbes, metals, pesticides and bacteria, and also can "fingerprint" samples using HPLC to compare an extract with others. Cost is between $l00.00 and $200.00 per sample per test.

VIII. Biocides (Natural Herbicides, Insecticides and Fungicides) and Anti-Phytovirals

Introduction

Lichen, leaves and roots of plants, fruit, dead insects, ocean sponges, microorganisms and a host of other natural sources can all be a source of chemicals, fungi or bacteria which can aid in the battle against insect pests, fungal invasions and other plant diseases. Success, a newly-approved natural insecticide from Dow AgroSciences, was developed from a pest-fighting bacterium discovered in soil samples from the Caribbean. In BC one group of researchers associated with BC Research Inc. has been examining the inhibitory activity toward fungal plant pathogens of microorganisms associated with Douglas-fir roots (Axelrood *et al.* l996). This group scrutinized l,820 bacterial strains established from the roots of Douglas-fir seedlings and found that two hundred and thirty four of these inhibited the growth of *Fusarium, Cylindrocapon* and *Pythium* spp. in *in vitro* assays. They also found that a significantly greater proportion of bacterial strains from actinomycete genera exhibited antifungal properties as compared with bacterial strains from nonactinomycete genera and that forty eight percent of all tested strains also inhibited one or more human pathogens.

Often insecticides and pharmaceuticals come from the same natural source.

Some of the botanical pesticides contain toxins as deadly to people as the synthetics, but the current search for biocides is based on *biological exceptions*. In the words of Murray Isman, a UBC scientist,"…Chemically-mediated insect-plant interactions in nature are far more subtle (than the actions of neurotoxins). Most plant defensive chemicals discourage insect herbivory, either by deterring feeding and oviposition (the placing of eggs) or by inhibiting larval growth, rather than killing insects outright. Thus the search for botanical insecticides with bioactivity comparable to that of synthetic neurotoxic insecticides is a search for biological exceptions." (Isman l994). A strong growth inhibitor, for example, which prolongs a pest's larval stage could serve as crop protector, since it increases the natural hazards to which the larvae are exposed.

Most currently-available synthetic insecticides poison insects' nervous systems. But these organochlorines and pyrethroids act equally well as synaptic poisons of insects or humans. Alternate materials currently under investigation include behaviour-modifying substances such as pheromones, kairomones, repellents and anti-feedants; biorational insecticides such as growth regulators and chitin synthetase inhibitors, and other botanical insecticides All of these emerging insecticides are distinguished from conventional chemical insecticides by these facts: they may target a single species; they require very low volume applications, and their actions are totally different. (Isman unpublished).

Substances Which Modify Behaviour

Pheromones –chemicals from indigenous insects used to communicate within a species—are widely used now in pest-management strategies to monitor populations. They can also be sprayed onto a field to confuse the males in their search for females. One group of widely-investigated pheromones are oxidized monoterpenes, which control some interactions of bark beetles with host trees (Buyers l989). Some pheromones which elicit an immediate response in insects are called "releasers" and those which stimulate long term responses are called "primers". A primer pheromone called locustol when released among locusts stimulates a transformation from solitary to group form.

None of the pheromones discovered to date are toxic to vertebrates and some are even used as cosmetic bases. Most are highly volatile and must undergo controlled release when used commercially to maintain persistence.

Kairomones are chemicals used to communicate between species, in which the "messages" are of benefit to the receiving species –for example plant volatiles which attract insects. Kairomones can be placed in traps with toxic chemicals, therefore minimizing the application area of the chemical. Pheromones, kairomones and allomones are all termed *semiochemicals*

Biorational Insecticides

These insecticides interfere with physiological processes unique to insects such as moulting and metamorphosis, both under the control of the endocrine system. They have no vertebrate toxicity and two types of insect growth regulators have been commercialized to date: chitin synthetase inhibitors and juvenile hormone mimics. The endocrine controlled moulting and growth in insects have been extensively studied and many substances have been found which interfere with these processes which were extracted from higher plants. In addition, phytochemicals such as pyrethreum, neem and rotenone have a long history of use, and many other plant chemicals with anti-feedant properties have been isolated. For example an extract from *Ajuga remota*, an African tree, completely inhibits the feeding of desert locusts at a concentration of 0.06ppm (Kubo, I. and K. Nakanishi l979).

Natural sources for medicines often contain insecticides. Therefore to achieve efficiency of effort, pharmaceutical testing of BC natural sources should be piggybacked onto insecticidal testing of the same substances and their sources. To give but three examples, the most prevalent medicine and insecticide source in the developing world is the Indian neem tree, *Azadirachta indica*. Used for over three thousand years for medicine and insecticides, the first isolation of the triterpenoid, azadirachtin occurred in l967 by E. D. Morgan (Butterworth and Morgan l968). Azadirachtin is the most insecticidally active of more than 70 triterpenes in neem and was finally isolated because it was a good antifeedant against desert locusts, and this fact revitalised the investigation of non-toxic crop protectors based on feeding deterrence.

Another example of this dual nature is tall oil, from which Forbes Medi-Tech is extracting phytosterols which they sell as both pharmaceutical and nutraceutical. Tall oil contains also diterpene resin acids which are an effective biocide (anti-feedant) against variegated cutworm (Yongshhou *et al.* 1993). A single depitching operation in BC can presently produce around 25,000 tons of tall oil and with a current price of around US $0.l0/kg. This is three thousand times less expensive than commercially available neem extracts.

In another case, an extract from the most widely used medicinal botanical in Germany, *Ginkgo biloba*, has been found to have potent insecticidal effects against brown planthoppers (*Niliparvata lugens*), a major rice pest.

As is the case with bioprospecting for pharmaceuticals among BC natural sources, the search for biocides will also be facilitated first by ethnobotanical searching, and given the commercial necessity of an on-going availability of source material to develop products, the initial searches here should be concentrated among the other "waste" products of our forest industry, including seeds and bark, sludge, oils, and any other wood wastes.

Given the above mechanisms of plant-insect interactions, Isman proposes a bioassay strategy focussing mainly on the physiological effects against insects –including growth disruption, growth inhibition and also acute toxicity. Incorporating plant extracts or isolated compounds into diets is a usual means of determining whether they inhibit larval growth. "…but because any bioassay where insects are orally exposed to test substances does not discriminate between growth inhibition mediated by behavioural deterrence (i.e., antifeedant effects), positive results need to be confirmed by a separate bioassay (e.g., topical application) where the results cannot be confounded by feeding behaviour." (Isman unpublished).

Markets for Biocides

Although the era of chemical-based pest management is rapidly coming to an end, biological and natural controls of crop and timber pests have yet to achieve anything near their potential, and the US market for natural products which can defeat harmful insects without wreaking havoc on humans, animals, useful insects or soil is estimated at only around US $250 million, as compared with average annual US expenditures of US $10-$12 billion on pest-killing synthetic chemicals (LA Times, May 4, l998).

The world's biocide bill is growing at a rate in excess of fourteen percent per annum (greater than the growth of the synthetic pesticide market, which is around US $32 billion annually). Even so there is still a lack of public funding, with less than ten percent of the USDA's research scientists and less than ten percent of their US $745 million annual research budget centering on natural methods of crop protection. A similar situation prevails in Canada. At present, botanical insecticides represent only between one and two percent of the world's insecticide bill. Nevertheless at the current comparative growth rates, biological and natural controls will entirely replace synthetics within two and a half decades.

In Canada under the Pesticide Control Product Act, all pesticides (toxic or otherwise) must be regulated and have a PCP (pesticide control product) number. Such entails a company expenditure of between Can. $500,000 and $600,000 in research and processing costs per product to determine efficacy and safety. One Canadian company applied for a PCP number for a neem-based product in l992 and still has not completed the process.

There are equivalent product introduction costs in the US but the EPA has recently introduced the category of "reduced risk pesticides", which involves reduced expenditures. These matters are analyzed in the policy sections.

Biocides and Biological Control

Before the deluge of synthetic chemicals after WWII, farmers generally used nothing but natural methods for crop protection, but once on the market, North America widely embraced neurotoxic chemicals as a pest-killing panacea in agriculture, forestry, and home gardens. As a result, once vulnerable pests have developed immunity to many chemicals, and although pesticide use in BC has significantly decreased during the past two decades, farmers in developing countries today must apply two to five times the quantities of pesticides to achieve what a single dosage accomplished in the early seventies, and excessive applications of neurotoxic pesticides have resulted in many documented cases of animal and human deaths, depleted soil and contamination of drinking water.

But most botanical insecticides are environmentally non-persistent and act through being "stomach poisons". They are not toxic to contact but must be ingested by the target insect to work. Thus natural enemies are not killed through contact with the sprayed flora as usually happens with the synthetic such as pyrethroids.

At the same time, big agricultural and chemical companies used genetic engineering tools to develop plants which can tolerate herbicides such as Roundup from Monsanto Co., and producers of pesticides have heavily invested in such technologies to ensure an expanded market for their existing chemicals.

All of this eventually had effects. In l996, the Environmental Protection Agency in the US, under the Food Quality Protection Act, eliminated the usage of many popular synthetic pesticides, and the US Dept. of Agriculture and the EPA have stated that by 2000, seventy five percent of all US crop acreage must have strategies for "integrated pest management", including methods which prevent infestation plus biological controls to stabilize pests to acceptable levels.

Here there is a variety of strategies ranging from the introduction of natural insect and bacterial predators of pests, while hoping they will not do worse things, to the disruption of sexual scents called pheromones to the introduction of non-toxic phytochemicals which more directly interrupt reproduction or introduction of soil microorganisms.

These rulings have motivated industry to renew their investigations of non-toxic phytochemicals, and to revive old concepts such as "male disruption". Male and female moths, for example, do not congregate, but when the female is ready to mate she emits an odor called a pheromone, which the male follows. Hundreds of such sexual scents or pheromones have been identified. Since they are expensive to synthesize, only about a hundred have been replicated in the laboratory.

Pheromones may be sprayed onto crops with aerosols and the males are unable to find the females. Other strategies use "attraction semiochemicals" to lure pest insects to sticky traps and to monitor populations. Phero Tech Inc. is a world leader in developing tree baits based on attraction semiochemicals. These baits work through containing and concentrating, for example, forest bark beetles within prescribed boundaries. The company also uses "anti-aggregation semiochemicals to reverse mass attack signals used by many species. With many host trees, a mass attack is required for pests to overcome the host's natural defenses, and natural antiaggragants can ward off or repel attacks.

Pheromones derived from local insects, in short, can be used to protect tree species, agricultural crops, grain storage warehouses, greenhouses and feed mills

BC Biocide & Biocontrol Industry

This sector is comprised of nine firms, four which raise biological control agents (insects which attack pests), one phytodiagnostic firm, two which are concentrating on pheromones – Phero Tech and a startup subsidiary of an Oregon Company, IPM Technologies Canada, and two pharmaceutical companies. There are also several US companies selling pheromone lure products in BC and several small, independent operators which produce pheromone products (for controlling coddling moths for example). Excluding the two pharmaceutical firms which produce in this sector also and for which revenue and employment figures have already been aggregated, this industry employs approximately l50 people and had l997 collective revenues of around Can. $10-$12 million. The industry sells its products and services mainly in the US and Canada.

Another strategy is to simply introduce natural predators of pests to agricultural crops and forests. If the stock for these natural predators come from BC wildlands, then they are within the product definition of this study.

Around the turn of the century until the advent of DDT, Canada was a world leader in the development and use of biological controls. Today Applied Bio-Nomics of Sidney is involved in the rearing and research of biological control agents for use in agricultural crops and has concentrated on predatory and parasitic species of insects and mites. Together with another BC company, Nature's Alternative, they currently raise about eighty percent of all control insects in North America. Both companies get most of their stock from BC wildlands. Other BC biocontrol companies include Coast Agri and Kopert Biologicals, a large European multinational with operations all over North America.

In other developments, AgraQuest, a California start-up has two natural product fungicides in the pipeline to be released onto the market within two years, designed to control brown rot, gray mould, brown rot, mildew and other fungal invaders of California's fruit, vegetable and nut crops. They are anticipating a world market of US $50 million for these two products alone. (G. Myers, personal communication). AgraQuest is three years old and its only commercial product at the present time is Laginex, which kills mosquito larvae and which was founded on an extensive search for promising fungi and bacteria in soil and lichens.
In short, emerging biocide technologies include: new commercially significant products containing insect juvenile hormones, insect pathogens such as *Bacillus thuringiensis*, the biochemical pheromones described above, insect viruses, predatory wasps and nematodes, natural plant growth regulators, microbial toxins, semiochemicals and natural plant extracts.

Since these new biopesticides have generally highly specific applications, potential sales of each new product is quite restricted compared with sales for a typical synthetic chemical, and many biocides are required to match the sales of a single synthetic chemical.

BC Biocide and Biocontrol Research Effort

Most of the research effort here has occurred in the public sector. In BC the following research projects are on-going:

J. Borden, G. Gries, K. Slessor and their colleagues at SFU's Centre for Pest Control are currently: using GC-EAD technology to identify bark compounds in six species of non-host trees –*Populus tremuloides, P. trichocarpa, Betula papyrifera, Alnus sitchensis, A. rubra,* and *Acer macrocarpa* - which are potential repellants of bark beetles, terminal weevils, ambrosia beetles and various species of cerambycid and buprestid woodborers. They are using similar methodology to identify host attractants of terminal weevils and woodboring beetles, and conducting field experiments testing the ability of non-host volatiles to inhibit insects from responding to attractant-baited traps.

This group is concentrating on the identification of new pheromones of insect pests of forests, seed orchards and nurseries and determining the efficacy of non-host volatiles to protect trees and logs from insect attack. The group is also providing on-demand research with a variety of companies –mainly concentrated in the areas of developing operational protocols for the use of repellant non-host volatiles in managing forest pests and developing new tactics for the use of attractive semiochemicals to manipulate insect populations.

The group has recently completed three years of field experiments in which pheromones of two bark beetle species , *Ips tidens* and *Drycoetes affaber*, were successfully used to cause **competitive exclusion** of spruce beetles. Spruce beetles and western balsam bark beetles are a real threat to old-growth spruce/balsam forests in the interior. These forests must be preserved for minimally three decades before second growth forests are large enough, and several forest licensees are considering the use of semiochemical-based **containment** and **concentration** programs before logging, so the beetles are pre-removed from the forests.

With the discovery that non-host volatiles could act as repellants, plus the discovery of new attractants for some beetle species, the group is also attempting to implement a **push-pull** tactic for beetle management.

Specifically the group is also involved in identifying the sex pheromone of lygus bugs to create a synthetic hormone available for pest control in BC nurseries; identification, testing and development of the aggregation pheromone of the western conifer seed bug, *Leptoglossus ocidentalis*, an invader of conifer seed orchards; determining bioactive constituents of oral exudates of larval western spruce budworms, *Choristoneura occidentalis,* to see if they can be used as a behavioral disruptant of pests, and identifying the aggregation pheromone of *Trypodendron retusum,* which displaces *T. lineatum* as BC's major ambrosia beetle pest in the north.

The group is collaborating with Phero Tech. Inc., using coupled gas chromatographic-electroantennographic detection (GC-EAD) technology to speed the isolation of semiochemicals for pesticides for six species of bark beetles, two species of terminal weevils and species of woodborers.

D. Gillespie, and his colleagues at the Pacific Agri-Food Research Centre in Agassiz have been investigating natural enemies of twospotted spider mites for biological control for several years (Gillespie *et al.* 1997). Biocontrol of insect pests and mites in vegetable greenhouses traditionally has relied on releases of single natural enemies for each pest. However, these researchers have found that *Orius tristicolor* and *Orius cucumeris* can be effectively used simultaneously for biological control of western flower thrips in greenhouse vegetable crops. This group and colleagues (Gillespies *et al.* 1998) have also found that the predatory gall midge, *Feltiella acarisuga*, gathered from the Fraser Valley, was the most promising candidate of a variety of predators examined for biological control of spider mites on tomato crops. As part of this multi-year research project, the authors collected and examined more than l,500 specimens, representing 22 species in seven orders and fourteen families of predators of spider mites. The objective of this research was to select other natural enemies of mites which could replace *Phytoseiulus persimillis*, which is ineffective on tomato crops.

Robb Bennett of the BC Ministry of Forests has been examining the management of insects and diseases in conifer seed orchards through pheromone identification of the Spruce Seed Moth, (*Cydia* *strobilella*) and the Douglas Fir Pitch Moth (*Synanthedon navaroensis*) (Bennett l997). This research team has also been examining non-host kairomones, analyzing volatiles from deciduous trees, including trembling aspen, paper birch, black cottonwood and broadleaf maple. They have found that such compounds may be utilized to repel the Spruce Seed Moth.

Bennett has also been examining the role of nematodes for suppressing cone maggots in White Spruce Seed orchards through researching the persistence and efficacy of the entomopathogenic nematode, *Steinernema feltiae* strain 27 in suppressing the soil-based cone maggots when nematodes are added in mulch and placed in the orchard (Bennett l997a).

D.Quiring and J. Sweeney have also been evaluating the potential use of marking pheromones by cone maggots in BC seed orchards (Quiring and Sweeney l997) and S. Shamoun and a team from the Pacific Forestry Centre in Victoria have been investigating the use of two fungal parasites (*Colletotrichum gloeosporioides* and *Cylindrocarpon cylindroides*) as biological control agents of hemlock dwarf mistletoe (Shamoun *et al.* 1997).

J.Carlson of Phero Tech Inc. is researching improved pheromone tree bait for the Western Balsam Bark Beetle (Carson l997). This beetle, (*Dryocoetes confusus*) is the most destructive insect pest of subalpine fir in BC and in association with a pathogenic fungus, *Ceratocystis dryocoetidis,* vectored by the beetle, is responsible for the loss of millions of cubic metres of timber in BC's high elevation, interior stands. Tree mortality losses between l948 and l975 have been estimated at l5 million cubic metres by (Stock l98l).

Anti-Phytovirals

Beyond pests, plant diseases, just as human diseases, may be combated with forest-derived substances, and Christopher French (Agriculture Canada at Summerland), Delano James (Centre of Plant Health at Saanich) and Neil Towers of UBC are involved in research using anti-viral compounds extracted from plants and fungi for the diagnosis and control of plant viral diseases. (French and Towers l992, James *et al.* 1996).

To date few BC forest species have been examined as a source of inhibitors of plant viruses. But James, Towers and French have identified several phytocompounds which are partially effective in inhibiting viral diseases of commercial crops such as potatoes and fruiting trees, and it is expected that BC forests will yield additional compounds.

Presently the main commercial anti-phytoviral is a synthetic called ribaviran, which is mainly used to eliminate viruses from infected clonal breeding stocks. There are presently no practical, chemical controls for viral diseases of food crops in the field, and world estimated losses from plant viral diseases, based on extrapolations from Waterworth and Hadidi (l998), are approximately US $l5 billion annually.

This BC research effort on identifying naturally-occurring anti-phytovirals which can either eliminate or seriously inhibit plant viral diseases is concentrating on flavonoids, a large, diverse group of compounds found in all plant species except algae. Flavonoids have well-known antiviral activity against a range of animal viruses. Quercetin, for example inhibits herpes simplex virus, pseudorabies virus and Mengo virus-induced encephalitis. (Beladi *et al.* l977) and 3-methoxylated flavones inhibit both poliovirus and rhinoviruses (Castrillo *et al.*, l986). But the latter group of viruses resemble plant comoviruses in both structure and genome organization.

French, Towers and James have examined the effectiveness of several flavonoids as anti-phytovirals, concentrating on derivatives of quercetin against tobacco mosaic virus (French *et al.* l99l) and potato virus X. Also, supported by an NSERC strategic grant, this group has investigated two additional viruses from different viral taxonomic groups: tomato ringspot nepovirus and apple stem grooving capillovirus. The group tested the effectiveness of forty eight flavonoids against the infectivity of ringspot nepovirus and found that twenty seven of these had antiviral effects, the most effective compounds being quercetin and ombuin. (Malhotra *et al.* l996).

The group also has tested the hypothesis that a combination of therapeutic agents such as flavonoids and ribavarin might prove more potent than a single anti-viral agent. (Ribovarin is a broad spectrum antiviral compound with activity against a range of animal and plant viruses but which has the disadvantage of phytotoxicity when used alone). The group found that a combination of quercetin and ribavarin successfully eliminated the apple stem virus from infected apple meristem tip cultures, and that quercetin, which has no inhibitory effects alone, significantly enhanced the anti-phytoviral effects of ribavarin as used in combination. Samples treated with ribavarin/quercetin tested negative after culturing on plain medium without antiviral compounds for several months, This apple virus is one of the most difficult to eliminate and this success shows considerable potential for other fruit tree viruses. An additional benefit of this work was the production of viral antibodies which can now be utilized for diagnostic purposes.

Building on the above work, this group is attempting to entirely eliminate tomato ringspot virus from tissue cultures and produce virus-free plants, and to screen other anti-viral compounds, such as chalcones (another type of flavonoid) against nepoviruses (James *et al.* l997).

In summary there are presently no effective anti-phytoviral chemicals commercially available in the world which can eliminate viruses from plants or trees growing in the field, and investigation of BC wildlands substances could possibly yield antiviral agents and novel diagnostic tools to determine the presence of viruses in potato plants, fruit trees and ornamental trees. Compounds which can eliminate viruses from propagation material which has been contaminated would financially benefit exporters to meet the phytosanitary specifications of the importing country.

There are no BC firms currently producing anti-phytovirals, but if compounds can be found which can eliminate viruses from infected plants and trees growing in the field, the annual world market would be approximately US $8-$10 billion within two years. The Ginseng Growers Association of BC is building an herbal processing facility in the Kelowna area which will be sophisticated enough to extract flavonoids and has expressed interest in so doing. Of all the non-timber forest industries, this sector involves the highest risks in terms of product development and largest potential payoff. The small BC research effort should be rapidly expanded through more generous funding.

Part II. The Economic Strategy

Introduction

The non-timber forest industries reviewed in the first part of this work employed almost 32,000 people in BC on a seasonal or full-time basis during l997 and were responsible for direct corporate revenues of approximately $280 million and provincial revenues in excess of $630 in that year. These industries were: ecotourism, floral greenery, wild food and medicinal mushrooms (or *mycomedicinals*), pharmaceuticals and nutraceuticals from plants, bark, lichens, wood waste and soil organisms; biocides (non-toxic insecticides) from the same sources, anti-phytovirals (medicines *for* plant diseases) and wildcrafting (foraging) for medicinal botanicals. This figure of $280 million does not include the revenues from native plants taken for rehabilitation, restoration and ornamental purposes nor does it include revenues from BC's manufacturers of herbal medicines and food supplements (since they presently use so few indigenous ingredients). The figure also does not include sales of essential oils used in perfumes and aromatherapy –both significant growth areas. The Europeans, for example, have large plantations of Sitka spruce, Grand fir and Douglas fir from which they extract oils for perfumery. The annual revenue growth of these industries varies widely between and within sectors, ranging from yearly averages of around l0%-12% for some of the wild food mushrooms to in excess of 30% for several of the nutraceutical manufacturers.

When BC exports are analyzed, it is often noted that resource based industries generate in excess of three quarters of our merchandise exports and that we need to facilitate economic diversification so that BC becomes *less dependent on* resources as sources of export earnings.

We are suggesting that BC become even more dependent on resources for export earnings through aggressively supporting the development of these emerging industries. These resources are not our "dependence". They are our *comparative advantage.* Several of the emerging sectors detailed in Part l such as nutraceuticals, phytopharmaceuticals and biocides, are, in fact, *knowledge-based resource industries.*

Some of these industries use advanced technologies in their discovery and manufacturing processes. Some are very low-tech. It does not matter, because most of them gather or manufacture *comparative advantage products* from BC and the Pacific Northwest in general.

Our strategy then has two parts – strengthening the international competitiveness of our traditional forest industries, (mainly through smarter tree growing on a smaller land base) and simultaneously facilitating the emergence of these new industries which are generally based on ingredients in under story plants, lichens, insects, bark, soil organisms, fungi and other flora and fauna, and which until now have been generally ignored.

The l997 provincial revenues from these non-timber forest products and services are still small compared to those for timber and pulp and paper. However if we conservatively assume that collective revenues grow by a factor of ten over the next decade, then they will account for in excess of a third of the total forest-derived revenues as computed at pre-recession market prices and export levels.

Over the next decade there will be an explosion of emerging products and services from BC's forests – genetic material for foodstuffs, biocides, natural medicinal bases, new dental products, spermicides and non-toxic contraceptives, resins, gums and camphors, cosmetic substances such as bases for face cream, perfumes and hair tonics; preventative healthcare products such as the tsunami of nutraceuticals coming onto the US market, ecotourism, crop protectors such as insect exudates which repel birds, chemical detoxifiers for both industrial processes and human tissue, new building materials modeled on naturally-occurring forms and structures, medicinal mushrooms, anti-phytovirals, and phytopharmaceuticals for humans and animals. People will always need to build, but timber will be only one of these products.

During l998 BC's traditional forest industry lost an estimated $350 million, the third consecutive loss in three years. All sectors of the industry are now losing money, and during l998, ten sawmills, one plywood mill and one pulp mill closed either permanently or indefinitely, throwing l6,000 people out of work. Predictions of the Council of Forest Industries include an additional l3 sawmill closures during l999, with estimated further job losses of l0,000. (Vancouver Sun, December l, l998).

The current recession in BC's traditional forest industries is a result of restricted US softwood markets, recessions throughout the economies of Asia, low commodity prices, rising costs and regulations. But it also presages two structural shifts occurring within the forest economy itself –a shift from the exploitation of old growth timber to (hopefully) knowledge-intensive cultivation and production of secondary growth on a smaller land base, and a shift into the emerging product and service areas portrayed in Part I.

As we run out of old growth forests and as harvesters push into remoter areas, wood costs rise. Between l992 and l997, BC stumpage fees increased l60 percent and logging costs more than doubled due to increased costs of logging remote areas and other factors such as the introduction of the Forest Practices Code. As wood costs have increased, corporate profits have plummeted and currently the costs of capital in the forest industry exceed the sector's profits by around Can. $700 million annually as averaged over a single business cycle. (Price Waterhouse l997).

At the same time, the higher prices for BC products to cover higher production costs have encouraged a movement away from our conventional wood-based products. One analyst (Binkeley, l997) gives this example: "The high cost of solid-wood posts manufactured from old-growth coastal hemlock caused the Japanese to develop a five-ply, glue-laminated substitute that could be manufactured from cheaper second growth trees, Now that their housing industry has adapted to this new technology, it is unlikely to return to the traditional BC product, even if the price falls." The rise of substitute products and of wood from emerging regions, in other words, restricts price increases for our traditional wood products. In fact some of our traditional forest industries may never return to their former vigour. Throughout the tropical part of the world there are pulp mills coming on line which are based on European advanced technologies, driven by low wage professional labour and which process very fast growing species. How can Skeena and other BC operations compete with these?

Shifts in economic production can be either embraced, resisted or ignored. As we recognize these shifts, we must use emerging biotechnologies to produce more timber on a smaller land base and at the same time free large wildlands areas for the tended cultivation of the bases of these emerging forest products. It has been estimated that with improved silviculture BC could produce around l00 million cubic metres of timber (compared to a current allowable cut of around 70 million) on only about one third of our productive forest land (Vancouver Sun, December l3, l997). Using this approach, BC would have an area larger than Italy to employ for these other purposes. This will be a gradual process, and the main mechanism facilitating the shift involves the introduction of *cultivation forests* into the present land tenure allotment. These are discussed in the following sections, which first analyze sectoral strategic measures and then pass onto general tax and fiscal incentives which should be applied to all industries highlighted in Part I.

Pine Mushrooms

Given the growth potential for pines from BC, the generally underdeveloped state of the industry, a continuing strong price in spite of the Japanese recession and an expanding market, the provincial government should move aggressively to economically develop the pine mushroom resource.

The provincial government can enact measures in support of both increasing the demand for, and supply of, BC's premium pine mushroom, *T. magnivelare.* These measures can affect product quality, export volumes, product price and market size. For example we have seen in Part I. that at least part of the price differential between Canadian pine mushrooms and those of Japan and Korea is accounted for by the fact that in the latter two countries, pines are farmed in cultivation forests under stringent conditions which include control for insect infestation. Pine mushrooms in BC are attacked by several species of fly larvae and the subsequent discard rate by buyers down the line is a major factor in our comparatively lower prices. One evident solution to supporting price increases for the BC product would be to seek biological methods to control larval invasion of pines in the field. On the other hand, little is known about the role of fly and insect species in spreading the spores of *T. magnivelare,* and until these matters are understood, such control measures could prove disastrous. However a cheap, portable detection technology which could be used by both pickers and buyers to determine infestation would go a long way toward improving customer perception of the quality of our pines and hence toward price increases in Japan for our product. The government should consider partial subsidization of such development costs or at least fund a technical feasibility study.

In spite of a large potential BC land base compared for example to Korea for the cultivation of pine mushrooms, the industry is nascent here in relation to that small country's production, and the entire Pacific Northwest export of pines reached around 500 tonnes only in l995. In a good year, Korea exports over l,000 tonnes. Secondly, infrastructure investments in pines in relevant areas will substantially increase the value of stands with marginal value timber; for example, stands of coastal and alpine lodgepole pine are appropriate for pine mushroom cultivation forests and not much else commercially.

The continuing buoyant prices paid for BC pine mushrooms in Japan during l998 in spite of the economic recession in that country show how deeply ingrained in Japanese culture is the autumn consumption of pine mushrooms and illustrates how people, even in times of scarcity, are not willing to relinquish this very expensive but traditional cultural and culinary experience. Given the American middle class's penchant to adapt Japanese culinary themes, it is also reasonable to assume that the Japanese market sales will be gradually augmented by increased US consumption of pine mushrooms.

The BC revenues for pine exports to Japan plus other wild mushroom exports are currently around Can. $45 million in a good year and through volume, productivity and quality increases, these revenues could easily increase by a factor of five to six to around Can. $250 annually. Productivity and volume increases entail gradually setting up dedicated pine mushroom cultivation forests, increasing the areas in which pickers are allowed to collect, extending the areas where pines fruit, and most of all emulating some of the technologies and techniques used in the cultivation forests and experimental research areas for pines and mycomedicinals in South Korea, China and Japan.

Adaptive Research Effort

Much applied research has already been done on Asian sister species of our pine, and our research effort in BC should concentrate on adapting these technologies and agroforestry techniques for BC conditions and species – beginning with pines and truffles, given their high unit prices. In both Washington state and Oregon, farms for fir Christmas trees are inoculated with truffles for joint Christmas tree and truffle production. Similar businesses should be supported here.

The Asian cultivation techniques in pine mushroom forests include cutting shrubs and selected trees as a forest gets older to guarantee sufficient aeration and sunlight on the forest floor, changing the litter thickness and adding wood pulp waste, artificial irrigation tunnels or small plastic hoods over colonies of pines (called *shiros*) to control soil humidity and temperature, pest control, fertilization, and a host of other technologies to entice increased pine production *in-situ*. This is called agroforestry -- growing better what grows there already or growing new flora in the forest.

Widespread throughout the world, agroforestry would include both cultivation forests dedicated exclusively to pine maximization and cultivation forests in which both timber, mycomedicinals and pine mushrooms are grown and harvested in complementary ways.

The cultivation forests of Japan, Korea and China offer available, successful commercial models, technologies and techniques, many of which can be adapted for quality and volume increases of BC's pine mushroom and mycomedicinal harvest. To our knowledge, in spite of the potential value of this information resource, no one from the Ministry of Forests has visited these operations; therefore, the provincial government should direct the chief mycological expert associated with the Ministry to conduct tours of the cultivation forests and pine mushroom research facilities in Japan, China and South Korea. Emerging from these tours, the Ministry should publish an initial simple language document aimed at buyers, exporters, growers, pickers, and new ventures describing the techniques and technologies successfully used with related species in Asia and associated productivity gains, the applicability of these techniques for BC conditions and species, and specific agricultural techniques to maximize pine production here. The Ministry should then initiate a program of adaptive research designed to increase pine mushroom production in BC and contract much of it out to the private sector and research institutions.

In summary, since almost all the pine mushroom research has been performed on Asian species, the provincial government should fund efforts to (l) adapt the Asian agroforestry techniques and technologies for pines and mycomedicinals to BC species and conditions and (2) initiate new colonies of pine mushrooms into barren forests or plantations, thereby extending the area producing commercial harvests. For example, one line of research here is focusing on using plants colonized by pine mushrooms such as conifer seedlings for these purposes. (Wang in preparation, Berch 1996a, Fogarty l999).

At the same time, we still do not know yearly numbers and masses of pine mushrooms or mycomedicinals growing in BC; thus research is also necessary to create baseline estimates of fruiting to ensure that harvests are sustainable. These adaptive research areas hold the greatest potential for new jobs and products.

Set Up Cultivation Forests

In order for this lucrative mushroom industry to flourish, it must be practically recognized through incorporation into overall forestry planning The government should introduce on a gradual basis, both cultivation forests exclusively dedicated to pine mushrooms and those dedicated to the joint maximization of pines, timber and mycomedicinals, and make these commercially available, under a variety of arrangements, (including competitive bidding) to a wide variety of concerns –ranging from the private sector to community forest projects. (Presently the only crown lands with tenure over non-timber forest products are the new community forests). Cultivation forests should be initially selected from areas of highly productive pine stands, and when possible, these cultivation forests should be individually connected through corridors linking bottoms of valleys with alpine ecosystems (S. Gamiet *et al.* l998) Adaptive research on Asian pine productivity techniques should be undertaken in these cultivation forests but this research should, in any case, begin immediately in designated crown land.

Even if tended, the pine productivity gradually declines as forests age, but even so, in cultivation forests set up for joint timber/pine maximization, the following principles should be followed: (l) the length of rotation of the timber harvest in these comparatively small areas should be extended to exceed the period of real pine mushroom productivity. Clearcut rotation periods should be increased from the current l00 years to 250 years; (2) only small groups of up to ten trees, should be logged, thereby retaining around 70% of crown cover, allowing in filtered sunlight but not changing moisture and temperature levels at the ground; (3) use group selection to leave small canopy openings of 0.05 to 0.25 hectare which are optimal for pines, and space these about thirty years apart to permit regeneration; (4) When openings are clearcut, about a quarter of the full stand structure should be left in patches (S. Gamiet *et al.* l998). Many other effective agroforestry techniques and technologies for pines and mycomedicinals are available from the Asian cultivation forests.

In cultivation forests dedicated to joint timber/pine production, one must also ensure that a variety of large, old trees are retained to act as hosts for saprophytic fungi, including pines and some of the mycomedicinals suggested in Figure 7.

Support Private Sector Marketing in Japan

The provincial government should also seek to increase the demand in Japan for BC pine mushrooms through increasing consumer awareness of the products' existence and quality. A provincially-funded exhibition of industry participants touring four or five smaller Japanese cities would receive extensive national and local television and media coverage and be generally well-attended. This should be repeated about every four to five years.

Stemage

The setting up of cultivation forests for pines, using these for adaptive research into productivity increases and making these cultivation forests available to the private sector on a variety of arrangements forces us to rethink the notion of land tenure and to introduce the idea of "*stemage*"-- the forest botanical equivalent of stumpage -- a small amount paid to the provincial government per unit of forest botanical gathered from Crown land. Eventually it will be appropriate to set up a system for botanical stemage, but given the nascent nature of the non-timber industries, the government should forego such revenues for a decade or more.

Similarly owners of private lands merit compensation for the granting of collection rights to other parties. It will be difficult to set fair market prices for sales of permits or longer term leases because many hidden cost factors are involved and we have little experience. But revenues to the provincial government should at least partially cover the costs of tracking and management. With respect to land tenure, in South Korea, most pine mushrooms are cultivated in privately owned forests, and in the US, there is open access, with some forest jurisdictions charging small access or picking fees, (which have generally provided inconsequential revenues to tracking or conservation efforts). However clarity and security of access with respect to the cultivation forests are necessary to ensure the levels of investment eventually needed.

Track the Resource

Given the potential value of this resource to BC, the gathering and sales of pine mushrooms should be tracked; there is currently no way to obtain comprehensive data; therefore, the main suggestion of the Pine Mushroom Task Force of l995, that buyers of pines from crown lands be licensed, should be immediately implemented. A condition of licensing should be the weekly provision of this information: the species bought; date of purchase; the weight and grade purchased; the price paid per grade, and the buying station location. . Most buyers keep this type of information anyway, and to lessen the data burden, this information could be summarized over weekly periods. A fee should be charged to purchase the license with appropriate fines for non-compliance, and the government's objective should mainly be obtaining this tracking data. As the problems with licensing are ironed out, the system should be gradually extended to buyers of other forest botanicals from BC.

Help the Private Sector Build Local Processing Infrastructure

The provincial government, through its agricultural and technology support programs, should help the private sector to build pine processing and preparation facilities near some of the prolific gathering areas, starting with the north-west region. The better paying jobs here and those which can provide value-added employment to poor regional economies involve processing and marketing of mushrooms and not just their harvesting, which is often seasonal, low-paying and devoid of benefits. One major factor limiting the further growth of the Nass region industry is the absence of proper processing facilities. Since much of the gathering is done by transient efforts of large Vancouver-based companies, most wealth produced by the industry leaves the community, thus hampering the ability of northern businesses to generate jobs. Both primary and secondary processing of pine mushrooms can be done locally, directing job benefits to local communities and first nations. Eliminating infested produce, raw materials handling, processing for specific orders, preparing shipments for delivery and such can all be done more efficiently locally with the proper infrastructures, and local processing could shave a half day off of the transition time to Japan and further enhance product freshness, a major price factor. While these are lower-paying jobs and often seasonal, expanding the infrastructure for pine processing to mycomedicinals would create a new job source for small rural communities in several parts of the province.

Typically in the Prince Rupert Forest Region pine harvest, the mushrooms are trucked to the Terrace airport for shipment the next day to Vancouver. An overnight wait in such unrefrigerated conditions results in further spoilage. If the day's harvest is too large, the overflow is shipped to Vancouver by refrigerated truck, a twenty four hour trip which adds an entire day to the general four day trip from the Nass to Japanese consumer. But each day's delay results in an eight percent weight reduction from moisture loss and the mushrooms' flavour, texture and odour further decline.

Upon arriving in Vancouver, the mushrooms are taken to a processing plant where they are inspected, re-graded, cleaned, sorted and weighed into one and two kilogram baskets. They are then trucked to the airport and shipped to Japan. Performing all of this processing locally and direct shipping --Terrace, Vancouver airport, Japan -- would considerably lessen transit time.

In addition to the procedures involved in processing fresh pine mushrooms, there are other forms of processing which should also be locally done such as freezing, drying or salting in brine and which will enable BC producers to capture a larger share of the retail markets. Such local processing will also allow a certain flexibility in the timing of the harvest and minimizes the weather condition risks. But most importantly, to re-emphasize, the more processing done locally, the more jobs will be provided for local people, including first nations. With the ratification of the Nisga'a Agreement, this nation will own half of the pine mushrooms in the Nass Valley. Neighbouring first nations are lobbying for an even greater percent of the surrounding valleys' pine mushrooms, and the Gitxan Strategic Watershed Analysis Team (the Eagle Clans of Kitwanga and Hazelton) has been mapping mushroom harvest sites and examining effects of current forest practices on pine fruiting in their traditional territories. Also the Wilp Sa Maa'y (Ksan Nation) have been trying to set up a cooperative for pine harvesting. Many first nations in the north-west region are trying to understand how to maximize revenues from pine mushrooms on traditional land, and local processing facilities would serve the needs of both communities.

The comparative advantage of BC exporters of pines over the main competitor countries of South Korea and China, lies in the fact that our fruiting season starts earlier and lasts longer –from August through December. Thus Canadian products appear at a time of scarcity and because of the long

season, BC exporters can better control production costs and sell during the December holiday season (big in Japan) for high prices.
With down line processing, the market potential for pines is greatly expanded with specialty, high end pine box enclosed gifts, specialty grocery stores, Asian food processing companies, and Asian airline meals. Also with further down line extraction of volatiles from pines (which can be taken from the wastage which is currently thrown away) a further layer of additive markets opens up such as liqueurs with pine extract, pine extract flavoured beef jerky and many other food stuffs which Japanese and other Asian cultures enjoy with pine flavouring.

Nutraceutical and Medicinal Mushrooms

The wildlands of BC are abundant with nutraceutical and medicinal mushrooms which could be gathered, cultivated *in-situ* in the forest, perhaps injected into new areas, and sold in varying forms – fresh, dried, extracts, products. The current world market for such mushrooms is approximately US $l.3 billion, mainly in Asia, (compared to Can. $45 million in sales for BC wild food mushrooms in a good year). To compete with low cost producers in other countries such as China, BC should develop a "Made-in-BC" brand name with a reputation for pristine, fresh, organic produce and sell anywhere, but mainly into Japan and the US markets. In these markets, fresh produce in its natural form fetches the highest prices. A fungus such as Chaga (*Laetiporus sulphureus*) can be stored for only six to nine months in prepared form and six weeks or so in natural form. Extend the storage or shipping time more and price plummets.

Of all the species suggested in Figure 7, we need to know which will prove to be the most economically valuable in the markets of Japan and the US over the next few years, and of these, the species' biological productivity, the species' reactions to harvesting techniques and the best harvest practices, the processes according to which the species grow, timing of optimal harvest and sustainable harvest levels. (Virtually all of these issues are being examined for pine mushrooms by Oregon's Forestry Research Station, which is why, in the context of pine mushroom research, we have suggested that this work not be duplicated but rather that BC researchers mainly concentrate on adapting agroforestry productivity techniques from Asian operations for pines). Several of our Canadian mycomedicinals such as *Ganoderma applanatum and G. tsugae* may contain equivalent therapeutic ingredients as such Asian "best-sellers" as *Ganoderma lucidum*, and could therefore be promoted world-wide as the BC Reishi. The government therefore should fund laboratory analysis of the ganoderic acids, triterpenes, polysaccharides and other ingredients in selected BC medicinal and nutraceutical mushrooms and, since consumer awareness of research partially drives markets, help popularize the results.

In general, this marketing and investigatory strategy should be adopted across a wide range of forest botanicals and not merely mycomedicinals. Pilz and Molina (l996) write "Given the receptivity of the American public to innovations in consumption and marketing, the exotic traditions of other countries might provide marketing angles for culinary, medicinal, and horticultural commodities in North America or offer new markets for products abroad. Species such as serviceberry, madrone, dogwood, hawthorn, wild rose, elderberry, mountain ash and viburnum have relatives native to Europe and temperate Asia that already are widely used".

The Commons and Cultivation Forests

The nutraceutical and medicinal mushrooms are less known than the pines. Unlike pines, it may be the case, for example, that some of these species cannot be sustainably harvested on an annual basis. The nutraceutical and medicinal mushrooms raise the problem of the commons. We are currently treating non-timber forest products such as pines as if they were non-market goods. They are market goods and it is reasonable that the provincial government eventually collect a small fee from each unit volume or unit weight of forest botanicals gathered on Crown lands.

The problem of the commons is this: If a single group of harvesters cannot plan all the harvesting activities on a single stand or piece of land, then one loses any incentive to sustainably harvest, because other people will continue harvesting after the first group has finished. This problem does not arise with pine mushrooms because most available mushrooms are taken and pines fruit the subsequent year anyway. This is the single most crucial issue of developing forest botanical industries in BC and one addressed by introducing cultivation forests into planning. Presently in BC we have conservation forests (parks) and areas used for timber in various ways. The former are meant to be absolutely natural areas, exclusive of all commercial development, but unless we introduce a third category, cultivation forests dedicated to the enhancement of commercially valuable forest botanicals, our understory plants and fungi are likely to be lost in the timber harvest.

Cultivation forests, beginning with pines, nutraceutical mushrooms and mycomedicinals, and administered through a series of formal leases which have boundaries clearly specified, are a necessary first step in long term economic management of BC forests. Many of the nutraceuticals and mycomedicinals will thrive in the pine cultivation areas, or it may be the case that techniques for pine enhancement harms some of them.

In summary the notion of cultivation forest involves the assigning of custodial harvesting rights to a designated extractive reserve for a single resource or related resources for a specified period. If cultivation forests are rented only to companies with the financial resources to develop these and with the objective of maximizing governmental stemage fees, wildcrafters and rural people will not be the ones who get the leases and will be excluded. Since it is part of provincial policy to try to diversify poor rural economies in BC, below-cost leases for some of the cultivation forests should be reserved for local small businesses, community forest groups and special forest products cooperatives, which should be supported through a variety of means. Coops encourage entrepreneurship among local peoples who have been excluded from developing and marketing products.

At the same time, wildcrafters will continue to gather on ordinary Crown forest land and planning must recognize that many forest botanicals cannot be gathered annually and still have commercial yields. For some species, it is therefore reasonable, as noted, to stagger gathering privileges in a specific region for two to three years. All of this presupposes we know a great deal about the biology of wildlands botanicals. We actually know comparatively little, even about the well-established wild food mushrooms. Washington State, for example, lost the German market for chanterelles more than a decade ago when there was a sudden, unexpected collapse of the stock one year. Rapid inventories, then, should be done of BC's stock of selected nutraceutical/medicinal mushrooms and other medicinal botanicals. If we do not know how stock levels are going to change, forest managers cannot implement adaptive strategies to produce sustainable levels to a rapidly developing market. These managers will have to make day-to-day decisions concerning allowable harvest in a certain region, number of foragers permitted there, length of the collection period, and related matters. The demand for these myconutraceuticals and mycomedicinals will arise as suddenly as the search for yew bark swept BC. We are totally unprepared.

Wildcrafting of Medicinal Botanicals

Given the small number of commercial collectors, the diversity of the resource and rising prices, this sector can only grow. Since unlike the case with mushrooms, the entire plant is taken with many medicinal botanicals, the main danger is stripping a species to extinction.

In terms of controlling quantity and quality of the harvest, it is certainly preferable to grow medicinal botanicals (or fungi) either on agricultural land or *in situ* in the forest (agroforestry) than to forage for them. A. Gunner (l998) has recently produced a manual for growers of medicinal and aromatic plants which can be grown in the Interior of BC. With each species discussed, Gunner has provided information on world production and demand, cultivation techniques, processing methods, active ingredients, buyer price range and production costs, risk estimates, profitability, and a listing of actual buyers of that species. Her species listing includes many indigenous BC plants, and the manual was initiated to address a lack of market information “at the production level” for medicinal and aromatic plants. BC growers need to know: where the markets are, the volume of production and demand for each species, stability and levels of prices, levels of “active ingredients” sought, distribution options, and the risk and profitability of certain crop mixes.

Thus in terms of controlling growing conditions and quality and quantity of harvest, cultivation is economically advantageous to wildcrafting, in which one is dependent on the vicissitudes of nature. But although several growers and nursery owners regularly wildcraft for St. John’s Wort and other botanicals, the people who wildcraft are generally not going to become growers, and both industries can coexist. Properly supported, collective revenues from the wildcrafting of medicinal botanicals alone could easily rise from their present annual level of between $2 million-$3 million by a factor of ten to the current revenue levels for pine mushrooms.

Beyond the potential commercial value of wildcrafting, -- the ceremonial gathering of medicinal and sacred plants, bark and other flora -- goes to the very heart of first nations cultures and beliefs and is a right guaranteed by the Constitution.

All the previous suggestions made within the context of nutraceutical and medicinal fungi apply as well to medicinals from plants. Starting with St. John’s Wort, Oregon Grape, Cascara, Devil’s Club, and plants going extinct such as *Cypripedium pubegens,* the government should document and map locations of the species of Figure 9, and make informed estimates of the amounts of each species growing. Again, with these species we need to know their biological productivity, their reactions to harvesting techniques, and the best harvest practices with respect to timing and optimal sustainable levels.

Given that consumer awareness of research results partially drives nutraceutical markets, the provincial government should try to direct appropriate federal research funds into the area of testing the efficacy of wildlands-based medicinal and nutraceutical botanicals from BC, in particular some of those used by first nations. It may be possible for example, to establish a significant, differentiated US and Asian market for BC Devil's Club as a wild ginseng substitute, but only with significant government promotion and market development activities
Many of these species have been extensively studied in both Europe and North America and again as much of this research as is possible should use these secondary sources. Using this information, the provincial government should produce guidelines, standards and field guides for the sustainable harvest of wildcrafted botanicals.

Since so many of the emerging non-timber products will come from the waste of traditional forest products such as bark, the government should expand the wildcrafters' access to this waste through; guaranteeing use of appropriate logging roads; and developing strategies and procedures with timber tenure holders to facilitate access by wildcrafters to understory plants before any clearcutting and to wastage after cutting.

Attracting Investment

Noting that BC presently does not have a "clear or coherent" strategy for attracting investment, nor have the private and public sectors cooperated effectively in this effort, a recent BC business "summit" has proposed that the provincial government work with the business community and other stakeholders to set up an *investment partnership board* which would market BC internationally as an attractive business location. We support this suggestion, and one area of emphasis of this board should be the emerging non-timber forest sectors with high annual growth rates – nutraceuticals, phytopharmaceuticals, herbal botanicals , mycomedicinals, biocides and ecotourism.

Agroforestry Incentives

Agroforestry involves not merely the gathering of non-timber forest species which naturally grow in a setting (salal, wild mushrooms, Devil's Club) but the cultivation and enhancement of these products in forest settings to improve their quantity, quality or sustainability, (for example irrigating salal). It also may involve the introduction and tending of understory species into a new area (for example injecting mushroom spores into logs). It might involve the simultaneous co-maximizing of timber and pine mushrooms in a designated cultivation forest.

But some current BC legislation and policies discourage agroforestry; many agroforestry products are not recognized as agricultural crops by the BC Assessment Authority's Land Classification/Taxation scheme and hence do not receive lower agricultural land tax rates; and some of the rules of the Agriculture Land Commission and the Forest Land Commission are prejudicial against agroforestry efforts.

Adequately addressing agroforestry concerns in the tax structure requires a more subtle approach than the traditional split between forestry and agriculture. The provincial government should therefore

conduct a tax review of the above matters, first determining which of BC's existing agricultural programs and incentives should be applicable also to agroforestry operations and then review tax/fiscal mechanisms and programs from other countries and regions of Canada presently used to preserve, consolidate or extend farmland, which could be modified to include land utilized for agroforestry. (BC's existing programs include the National Income Stabilization Account (NISA), the Whole Farm Insurance Program, the Canada-BC Crop Insurance Program, Grants for Replanting, Exemptions and Reductions of Property Tax, and the Interest Subsidies on Advanced Crop Payments to Growers (under the federal Advance Payments for Crops Act)).
The inclusion of agroforestry businesses in any pertinent BC legislation will involve revising the classificatory scheme for property in BC, an extended definition of Class 7, "Managed Forest Land", a more extensive application of the Split Classification, a revision of the assessment procedures and criteria, and revision of BC Reg. 4ll/95, "Standards for the Classification of Land as a Farm". The main objectives here are to revise the existing farm property tax concessions in such a way that they apply to agroforestry production, cultivation forests and such, and to accelerate the permanent or term classification of privately-held lands into designated cultivation forests.

Holm (l998) has written a comprehensive analysis of BC's agricultural policies and incentives as compared to those in other countries and regions and many of her recommendations may be applicable to agroforestry and cultivation forests, in addition to farmland. For example the Ontario experience with conservation easements of farmland is pertinent to the problem of motivating private landowners to convert portions of property into cultivation forests. An agricultural easement is an agreement between landowners and governments which restricts the use of the land to agriculture for a limited period of time (called a term easement) or indefinitely (a perpetual easement). In return the landowner receives tax benefits or direct payments. The perpetual easement is binding on all successive landlords. Properly written, such an incentive could be utilized to accelerate the rate of conversion of BC privately-held lands into cultivation forests.

Holm also recommends that BC revise the farm taxation/estate laws in such a manner that incorporates so-called "circuit-breaker" programs, as in the US. She gives these examples: Wisconsin since l977 has given farmers "circuit breaker" property tax relief via state income tax credits. "For every dollar of credit received, taxes owed are reduced by a dollar. Credits are triggered by pre-set income figures….The (specific) amount of the income tax credit depends on the level of property taxes and whether the county has agricultural zoning and an agricultural preservation plan. Tax incentives increase as farmland protection becomes stronger -- a farmer qualifies for 70% of the credit in a country with only agricultural zoning and for the full tax credit in a county with both agricultural zoning and a preservation plan. Further, the farmer filing for a tax credit in a county with only a preservation plan must enter into a ten-to-twenty-five year agreement requiring the land to remain in farming. If the farmland is rezoned or sold for a non-farm use before the agreement expires, the landowner must pay back up to ten years of tax credits." (ibid. p. 117). To date farmers in Wisconsin have enrolled around eight million acres in the circuit breaker program.

In Michigan this circuit breaker tax relief through refunds of state income tax is triggered if the local property taxes are greater than seven percent of the net farm income. By l998 Michigan farmers had enrolled almost five million acres of land in their program. We support this recommendation with the proviso that it should be applicable also to agroforestry practices in designated cultivation forests or on private lands.

The Regulation of Natural Health Products

As documented in Part I, BC has a gamut of species –ranging from fungi and soil organisms to vascular plants and insects -- which can provide the bases for a variety of natural health products. Presently there is a very restrictive regulatory environment which places BC producers at a distinct disadvantage with respect to those in other countries. However, on May l3, l998, the federal Advisory Panel on Natural Health Products released recommendations for a regulatory framework for natural health products, understood by the Panel to include "substances or combinations of substances consisting of molecules and elements found in nature, and homeopathic preparations, sold in dosage form for the purpose of maintaining or improving health and treating or preventing diseases/conditions." (Health Canada l998).They thus include homeopathic preparations, nutraceuticals, vitamins, minerals and enzymes, herbal botanicals, animal and insect source substances and a gamut of molecules extracted from natural substances such as amino acids, polysaccharides, triterpenes, peptides hormones and precursors.

These natural health products are viewed as neither really food nor drugs and the Panel has recommended this restructuring of concepts to specifically address natural health products –that the category of "drug" in the *Food and Drugs Act* be replaced by the concept, "Therapeutic Products in Dosage Form" and that the definition of the latter term be expanded to included the intended use of products to maintain wellness. The "Therapeutic Products in Dosage Form" section of the *Act* would then be divided into these categories – pharmaceuticals and natural health products, as defined above.

These shifts will set up a new liberalized regulatory framework to govern a wide range of natural health products in Canada. The key words are "in dosage form", since under these changes, (l) all products which are sold in dosage form, including nutraceuticals, domestically produced or imported, are covered; (2) functional foods and herbs used in traditional Chinese medicine, both sold in bulk, are not covered since they are not marketed in dosage form; (3) products for personal use are excluded from the definition, for example first nations' herbal medicines.

More importantly, the Panel has recognized that unlike synthetic pharmaceuticals, natural medicinal substances have a long history of use, during which time substantial bodies of knowledge have formed about many of them and that their regulatory assessment should rely on sources and forms of supporting evidence substantially different from that required for pharmaceuticals (double-blind clinical trials).

They have also recognized that most natural-sourced products are safe and should be allowed onto the market with a minimum of regulatory delay, that use risks can be mitigated by proper labeling or professional intervention, and that regulatory controls should not unduly restricts consumer access to these products.

Finally the Panel has recognized that any new regulatory framework must not add undue costs to marketing or market entry, and that cost containment is dependent on product assessments, which should be in reasonable proportion to product risk, which is usually very low. The Panel has therefore devised a new regulatory framework which is permissive rather than prescriptive, with minimal state interventions unless warranted by potential risks and independently administered by skilled persons in the field of natural health care.

Natural health products are permitted to carry *claims of health benefit* and most products would be eligible for marketing with merely a post-market notification to the regulatory authority. Three types of health claims will be permitted: "structure-function claims" which report a product's effect on a physiological function or structure of the body; "risk-reduction claims", relating product consumption to risk reduction for diseases; and "treatment claims", which report product effect on the actions of specific diseases or their symptoms. Most of the Panel also favored permitting sales of products with no explicit claims. Since present law dictates that therapeutic products be sold with no claims on the labels, it is not logical to exclude this option.

The vast majority of products can obtain immediate market entry but others would be subject to pre-market regulatory assessment by a new regulatory administration distinct from that for pharmaceuticals and foods, both of which are properly seen as inappropriate for natural health products.

Under the proposed regulatory framework, all natural health products sold in Canada or imported would have to meet certain standards of quality –users must be sure that what they read is in it actually is – and of safety. The Panel believes that the vast majority of natural health products can be described with "higher safety" (can be safely consumed without the intervention of a professional) if they are properly labeled. But certain products would be classified as "lower safety" for a variety of reasons: a narrow margin of safety between therapeutic and toxic dosages; potential severe side effects at normal therapeutics dosage levels; their use may mask other ailments, and so forth.

The Panel thus felt that present pharmaceutical regulations are inappropriate overkill when applied to natural health products, most of which are inherently safe and should not be subjected to expensive double-blind clinical studies.

Assuring basic standards of safety and quality is the essential factor in mitigating risks of consuming any product, and the Panel therefore recommended that Good Manufacturing Practices and processing standards be reviewed for natural health products; that all manufacturers, packagers, importers and distributors selling natural health products be licensed, the issuance of which would be dependent on compliance with GMP requirements, and that product labels and packaging carry the following minimal information: name, composition, directions for use, cautions and warnings, expiry date, storage conditions and a lot or batch number (to facilitate GMP controls and recalls). As noted, the *label, may also contain claims of health benefits or effects.*

The proposed licensing process is very simple –post-market notification for the vast majority of natural health products and pre-market submission of the others for review.

With respect to the latter process, manufacturers, importers and distributors of new products for which there are no standards or monographs or when the product is classified as "lower safety", must submit evidence to the regulatory authority to place their product on the market. This information would include product name and composition, traditional and cultural references, clinical evidence, published literature and professional consensus. If approved, the regulatory body would then issue a certification, which would include labeling requirements such as precautions, warnings, indications for use, and access restrictions. The regulatory body would assess the validity and credibility of data sources submitted for review, using a broad range of possible supporting evidence –traditional or culturally based references which are often based on centuries of product experience; published literature outside the mainstream scientific technical journals; and professional consensus.

Finally the Panel has recommended the immediate rescinding of the notorious Schedule A of the *Food and Drugs Act*, enacted in l934 and which lists certain diseases for which treatments cannot be advertised to the public, and the rescinding of other outdated restrictive legislation in the *Food and Drugs Act* itself.

In November l998 the Standing Committee on Health tabled "Natural Health Products: A New Vision", which takes up most of the above recommendations. But to date none of these recommendations have yet been passed into law and natural health products classified as foods still cannot make health claims concerning use or efficacy in either packaging or marketing. Products which do make health claims have to be regulated as drugs. This involves the provision of very expensive monographs or controlled clinical trials to obtain a Drug Identification Number and effectively stops many product developments. In the meantime Canadian vendors of natural health products remain at a distinct market advantage. This legislation is a good first start, and as the major Canadian source of medicinal and nutraceutical wildlands substances, BC should lobby for its rapid passage into law.

Commercialization Barriers to Biocides

If there are so many potential wildlands sources of biocides as discussed in Part I., why are there not more of them on the market? At present, the only widespread North American and European sales involve pyrethrum (from *Chrysanthemun cinerariaefolium)* and rotenone (from *Derris* and *Lonchocarpus* spp.). The use and sales of neem (*Azadirachta indica*) as an insecticide are just beginning in North America, although neem has been used for millennia in Asia for this and other purposes.

Beyond efficacy and species applicability, the biological criteria for a biocide involve non-toxicity for vertebrates, a selectivity which favours natural predators of the target insects or pollinators, and rapid degradation. In addition, commercialization barriers involve the comparative scarcity of the source materials, standardization of extracts and quality control of active ingredients, and regulatory approval (Isman l997).

Most biocides work against a narrow spectrum of insects or a single species or genus and small startups may therefore have limited initial markets for their product. Also companies have little economic incentive to develop new biocides unless there is a guarantee of a continuing source of starting material. The material can be wildcrafted, grown in plantations or *in situ* agroforestry projects, or produced through tissue culture, but significant amounts of it must be produced on an on-going basis. With respect to standardization and quality control, the natural defences of plants against insects usually involve a variety of closely related chemical compounds rather than a single ingredient alone and operate through a synergistic effect (Isman l997). In this respect they are similar to the alleged actions of herbal medicinals, from which they are often derived. Pyrethrum, for example, contains four insecticidal esters, and rotenone has at least six insecticidal isoflavonoids.

In many cases the net efficacy of the entire mixture is superior to the effects of the most active constituent alone. Chen and others, for example, have found that the effects on growth inhibition of entire extracts from bark of *Melia toosendan* which contained 60-75 percent toosendanin were significantly greater than those of pure toosendanin, which would indicate that minor components made a greater insecticidal contribution than their mass would indicate (Chen *et al.* l995).

There is also evidence that the chemical cocktails of entire extracts from botanical insecticides confer less pest resistance over many generations than the applications of a single active ingredient (Feng and Isman l997). This is an additional economic benefit because, as with phytopharmaceuticals, it is usually too difficult or expensive to isolate and synthesize principal active ingredients in biocides.

The main problem however arises with standardization. For regulatory and commercial purposes, biocides, like synthetic pesticides, must contain a specified level of active ingredient(s) to guarantee that products will perform as claimed. But how does one standardize a biocide which contains dozens of potentially active ingredients, whose effects may arise from their interactions and proportions? Pyrethrum is standardized according to the concentrations of two pyrethrin esters, but when six or seven ingredients are involved in the insecticidal effects and these effects arise from ill-understood interactive processes, the testing and standardization is prohibitively expensive. (For such complex mixtures acting on synergistic principles in which efficacy arises from many such “active principles”, standardization will probably eventually be based on chromatographic fingerprints of the entire material, thus creating a qualitative standard).

Assuming that standardization problems can be solved, required studies supporting regulatory registration of a new biocide in the US or Canada can cost between Can. $250,000 to Can. $2 million, and for small, start-up companies, no sales revenues can be generated prior to regulatory approval.

The regulatory protocols applied by Canada’s Pest Management Regulatory Agency (PMRA) were developed in the context of synthetic pesticides containing one or sometimes two active ingredients and are not remotely applicable to biocides. For example when one private company contacted the PMRA concerning a neem-based insecticide used for thousands of years in Asia, they were told to identify every component of the extract comprising at least 0.l percent by weight. There were thirty of these and such a characterization of a complex neem mixture might require a year or two and cost dozens of thousands of dollars to complete. (The PMRA finally approved experimental use in one case to spray neem extract for control of forest-defoliating sawflies after HPLC analysis identified and quantified the major ten limonoids.) (M. Isman personal communication).

In the US the EPA, recognizing that many of the constituents of biocides are benign, has admitted a category of “reduced-risk” pesticide, with reduced registration criteria. Although the EPA and the vendor company wish the products to have the same ingredients every time, there is also a recognition of chemical variations found in natural substances –that different concentrations and even different phytochemicals may be present in a plant depending on what time of year it is picked, where it grows, and so forth.

Even so, the costs of long term studies demanded by the EPA and the PMRA constitute a serious commercialization barrier to the small startups trying to manufacture biocides. One solution here proposed by Isman is to allow provisional registration in Canada of reduced-risk biocides in a geographically restricted area or restricted to low-risk uses. “Assuming the outcome of the acute tests is favourable, a provisional registration would allow the manufacturer to begin marketing the botanical insecticide…to generate revenue, with the understanding that the registrant would have to provide data for the long-term tests and other data requirements within a 2-5 year period.” (Isman l997).

In any revisions of the guidelines for biochemical pest control products, the following additional points should be taken into account. Although often one of the distinguishing differences between conventional pesticides and biochemical agents is that the former are acutely toxic, this definition is too broad to serve as a distinction to determine data requirements for registration. It is preferable to use a l988 FAO definition of biochemicals (FAO l988) as those which “exhibit a mode of action other than direct toxicity in the target pest.” Such a definition allows one to distinguish between most conventional insecticides (neurotoxins) and products which act by other means of actions such as insect growth regulators or inhibitory agents.

An alternate classificatory scheme could also be based on the main means of bioactivity. Thus one would have substances which modify behaviour such as pheromones, antifeedants and other allomones, and kairomones; and substances which act physiologically such as insect growth regulators. The problem here is that many plant substances have both types of bioactivity. Although a wide range of potentially insect-controlling plant substances show vertebrate toxicity, this is no justification to place botanical insecticides in the same class as synthetic chemical pesticides, because the former are safer environmentally for the reasons discussed in Part I.

Secondly, the excessive data requirements for registration financially stifle all but large multinational chemical companies which can afford to satisfy these, and one of the largest barriers in registration for small companies is the requirement for lifetime feeding studies of laboratory animals.

In summary, a potential solution to these problems involves a tiered approach to environmental and toxicological testing, with “the use of waivers for specific data requirements where an acceptable rationale can be provided” (Isman l997).

With the use of waivers, an applicant would have the option to provide reasons why a specific data requirement should be waived. The regulatory agency would then decide if the data requirements of concern should be actually required for a thorough evaluation of the substance. Rationales might include:

lack of toxicity for an entire class of compounds such as pheromones; lack of toxicity as evidenced through extensive use in other countries; action mechanisms unique to insects such as moulting inhibition, or alternate human uses such as medicines. (For example one can legally purchase and eat neem oil containing one percent technical active ingredient, but if one sprays the same product onto a commercial crop, one has broken the law).

What is needed is a review and streamlining of the national pesticide regulations as they apply to biocides which is as thorough and far reaching as the current revision of regulations applying to natural health products discussed in the previous section. (The federal government conducted such a review in the early nineties but not much came out of it).Again as the main Canadian source of new wildlands substances for biocides, the provincial government should lobby for such a review.

Tax and Fiscal Incentives

The heart of any economic strategy lies in the tax/fiscal incentives given to specific sectors or to certain activities, such as manufacturing startups or research, in all sectors of an economy. Given the lushness and diversity of BC non-timber forest resources and the nascent nature of the industries trying to develop these, how can we optimally apply the tax structure so they can rapidly grow?

When one looks toward tax and fiscal incentives to support these emerging industries, there are two kinds of measures: general taxation changes which would apply to all sectors of the BC economy and facilitate a more level playing field with competitor companies in other countries and provinces, and measures applied specifically to these emerging industries. In the following discussion we first analyze proposed general changes and then pass on to incentives to be uniquely applied.

Capital, Sales and Machinery Taxes

Corporate capital taxes are payable in most provinces and to the federal government when the amount of taxable capital at the year's end is greater than certain threshold amounts. This taxable capital usually includes the secured debt of lenders, the entire shareholders' equity, and any amounts owed to additional creditors and lenders which were outstanding for three months or more at year's end. This tax is payable to provincial and federal governments whether or not the company had any profits, but federal capital tax is always credited against federal surtax. Typically the provinces exempt the first $ l million to $ l.5 million of capital from this tax. The current rate is 0.3% of paid up capital. The capital tax rate in BC is high compared to tax regimes in the US, but the BC government is in the process of reducing the corporate capital tax.

At the same time, several provinces exempt some items from sales tax. BC, for example, presently exempts parts and materials for prototypes, livestock for human consumption, feed, seed, fertilizer, certain items in ore processing, certain exploration, drilling, energy conservation and safety equipment, software source code and "l-800" calls after May l, l998. With the exception of software source code, most of these items reflect policy makers' attempts to support BC's traditional forestry and agricultural industries. Several provinces, in addition to BC, have tax exempted "l-800" call service operations, which is what has been done in countries such as India and Bangladesh. It is more sensible to use our tax instruments to support BC industries exploiting our natural comparative advantages described in Part I.

We recommend that the BC provincial government exempt the provincial social services (sales) tax on all machinery and production equipment used for research, non-routine testing and analysis, and that used in new manufacturing startups – one wants to encourage companies to adopt new and more efficient production technology, not make it more expensive. If the recipient in question is a manufacturer, this incentive should be structured in such a way that exempted equipment can be used for a combination of research and manufacturing.

Canadian Federal R&D Tax Credits

Under Canada's federal R&D Tax Credit System, scientific research and experimental development (SR&ED) expenditures (both current and capital) are one hundred percent deductible. This discretionary deduction can be carried indefinitely forward, and investment tax credits (ITC's) from twenty to thirty five percent can be earned on SR&ED expenditures including salaries, materials used, wages, costs of leases for equipment, new capital assets used specifically for research and development, overhead costs, third party payments and contractors.

Large Canadian public corporations and multinationals receive a 20% non-refundable tax credit on SR&ED expenditures, and Canadian-controlled private corporations (CCPCs) with a taxable income less than Can. $400,000 may receive their credit in part or whole as refundable tax credits. The incentive is structured in this way to help the smaller Canadian companies' cash flows and give them direct rewards (rather than forcing them to accumulate credits until they are profitable and able to take advantage of the accumulated unused credits (Lipsett l997).

These federal incentive are among the most generous in the world and a company can be fully reimbursed by a foreign company for any R&D performed in Canada and still remain eligible for these federal R&D incentives.

This system maximally benefits CCPCs, (those not controlled by a non-resident or by a public company). Although non-residents are permitted to hold up to fifty percent ownership of Canadian controlled private corporations, they cannot be a subsidiary of a foreign controlled company. This structuring of the preferred tax credit rate has resulted in many US companies setting up a Canadian partner company.

Excluding rent, companies can conventionally compute their overheads or they may use a proxy method, according to which they can claim overhead equal to sixty five percent of all qualifying research and development salaries. Most emerging biotech companies interviewed in Part I. use the proxy method since this generates higher investment tax credits.

The problem with using the proxy method is: whose salaries are included in the claim? In the view of Revenue Canada, qualifying activities are: basic and applied research and experimental development and they are now demanding itemized documentation of employees' SR&ED activities (time spent on a specific project and the specific nature of the work). This forces companies to maintain rigorous time sheets which Revenue Canada then uses to classify salaries as “qualifying” or “non-qualifying”. Without extensive time sheets, Revenue Canada will disallow the claim. The provincial government should lobby Revenue Canada to streamline this process and make reasonable claims without the maintenance of such itemized time sheets.

Another feature of the SR&ED program is that all expenditures claimed must be for research and development performed in Canada. However, due to the nature of its business, often a company such as PheroTech must do their research for a client off shore, with indigenous insects in Texas, for example. But although the intellectual property base for that research was created in Canada, they cannot make a claim in this case. The province should lobby to alter this clause.

Most importantly, the nomenclature in terms of which this incentive is cast, “scientific research and experimental development” is intimidating to small companies and work which qualifies for the SR&ED tax credits must represent a “scientific advance”, involve technical risk and use scientific methods. What we should be concerned about here is support for simple research in product and process development, including incremental improvements rather than a “scientific advance”. This is what drives the economy and several analysts have noted that the federal credits tend to support scientific discovery of innovations and inventions rather than rapid adoption of manufacturing technologies from any source. (Quebec, for example, offers a l25% immediate write off on expenditures for the acquiring of intangible technology used in manufacturing).

Provincial R&D Incentives

R&D incentives are offered also by most provinces to compete with one another for foreign companies, to increase the density of professionals and other purposes. For example, New Brunswick and Nova Scotia have offered an additional ten percent non-refundable tax credit for qualifying expenditures and Manitoba offers fifteen percent. A comparative summary of Canadian federal and provincial R&D incentives is available on the KPMG website (l999). Quebec, it should be noted, offers a l00% SR&ED deduction on current and capital expenditures, and this amount is not reduced by federal tax credits.

BC presently does not have any R&D incentives.

Of particular relevance is Quebec’s refundable wage tax credit, which amounts to 20-40 percent on SR&ED wages incurred and paid in Quebec. In addition, Quebec offers a two year provincial tax holiday on Quebec salaries paid to foreign researchers. The latter incentive has been very successful in attracting foreign professionals and motivating foreign companies to move to the province, in spite of the political uncertainty. The more complex and comprehensive set of R&D incentives in Quebec also includes increased incentives for companies collaborating with Quebec universities.

Ontario’s Superallowance research deduction on top of the l00 percent write off of federal claims provides for 35 percent to 52.5 percent for CCPCs and 25 percent to 37.5 percent for other corporations. This superallowance has two components – base and incremental. All R&D performing companies in Ontario are given the base level R&D superallowance deduction from their income, and an incremental component which is calculated from the average R&D expenditures incurred in the three preceding taxation periods. All current and capital expenditures greater than the base average are considered to be incremental.

In addition during l997 Ontario introduced the Ontario Business Research Institute Tax Credit which pertains to research and development contract payments to Ontario post-secondary educational institutions, research institutes associated with hospitals and non-profit research institutions. This tax credit refunds 20% of a maximum amount of $20 million in qualifying expenditures annually.

Ontario's third main initiative, the Ontario New Technology Tax Incentive, offers a l00 percent deduction of up to $20 million annually for the purchase from unrelated persons of "qualifying intellectual property" –patents, licenses, permits, and know-how, and thus supports technology transfer from offshore sources.

Finally Ontario also eliminated the retail sales tax in May l997 on all R&D equipment bought by manufacturers or non-profit medical facilities. If the recipient is a manufacturer, such equipment can be used for a combination of manufacturing and R&D, but with medical research facilities, exempted equipment has to be used for R&D exclusively.

We recommend that the provincial government put into place a l0% tax credit on R&D, paralleling the other provinces. These credits should be refundable in the same way the federal credits are and to the same type of recipients, CCPCs.

A l0% increase will directly make little difference really, but its importance lies in the fact that it will be a clear market signal to the private sector that BC is concerned with private research and recognizes its role in economic growth.

A non-refundable credit is one in which the credit merely reduces taxes owed. A refundable credit not only reduces taxes owed but pays out the excess to the tax filer. Thus refundable tax credits are available to companies even if they pay no taxes. The federal incentive, we have seen, gives a refundable credit to Canadian controlled private corporations calculated as a certain amount of eligible expenditures and a non-refundable credit to other firms. Qualifying the refundable portion prevents large foreign companies from receiving large tax gifts from the public.

Thus the BC R&D incentive should parallel the federal structure, with the refundable portion capped at $2 million of eligible R&D expenditures (as in the federal incentive), and available only to CCPCs. The non-refundable portion should not be capped.

Paralleling the Ontario measure, we also recommend that BC offer a l00 percent deduction (capped at $20 million annually) for the arms length purchase of qualifying intellectual property such as licenses, permits, patents and know-how –thus supporting technology transfer from offshore.

We also recommend that BC offer a tax credit which can refund 20% of a maximum amount of $20 million in qualifying expenditures which pertain to R&D contract payments to post-secondary educational institutions, non-profit research organizations, and research facilities associated with hospitals.

Selective Professional Tax Deferral

BC is dense in natural resources but still thin in professionals. It is often claimed that the quality of life compensates professional talent from south of the border for the high personal and corporate tax burden compared to that of the US, (an estimated differential of 29%-44%, depending on how one calculates it, in real income), but all of the seven companies in Part I. producing phytopharmaceuticals and nutraceuticals have to cope with shortages of knowledgeable business managers and skilled people to bring products to markets. There is also a lack of professionals who can manage the diversity of activities involved in clinical trials and regulatory procedures. There are also problems in finding experienced lawyers who can beneficially structure partnerships and intellectual property agreements.

Although federal and provincial tax credits render the after-tax costs of R&D cheaper in Canada than almost any place in the world, the additional personal income tax paid by new employees from (mainly) the US is the single greatest recruitment issue. Another problem is that the federal R&D tax incentives are not linked with incentives to set up commercial manufacturing facilities (as they are, for example, in Quebec). *Therefore we recommend that the provincial government offer a two year provincial tax holiday on BC salaries and stipends paid to foreign researchers by Canadian-controlled companies, including legal research pertaining to intellectual property, regulatory procedures, and the management of clinical trials.*

Tax Holiday on Selected NTFP Industries and Services

Many economists believe that governments should not be in the business of selecting particular industries to support, and it has become popular wisdom that civil servants are not adept at "picking the winners". And yet organizations created by Asian governments, ranging from Singapore's National Technology Development Board to Japan's MITI, have often succeeded in doing so. How have they done it? The more deeply cooperative and less adversarial relations between the private and public sectors in these countries, and the authoritarian prerogatives of some of their governments, may have some explanatory power. There is, however, a more specific contributory cause. Korea, Japan and Singapore have made periodic efforts to help the private sector in identifying industries, products and new production technologies which might profitably be developed.

But often, by the time contemporary and future production technologies have been identified in government and academic studies, these technologies are three to six years old. Yet in 1979, the Singaporeans managed to identify software as a future growth industry in which they could excel when it was still generally given away, freely embedded in computers or written on an individual applications basis. They also identified other growth industries such as multimedia products and wireless personal communications in the mid-eighties before there was much development anywhere, and by l994 had realized that they could develop as a service centre for internet retail sales. Their accurate and profitable prognoses were arrived at by spending considerable sums of money and time consulting a variety of knowledgeable sources: industry participants, international consulting firms such as Arthur D. Little, Stanford Research Institute and the Boston Consulting Group, and active research firms such as Xerox Parc. (Singapore probably spent more than US$ l million in 1979-80 just in identifying computer software as a future growth industry.) Singapore then, first identified growth sectors pertinent to their comparative advantages, and then gave these very targeted tax advantages.

Within the restricted domain of BC forest industries, we have done the same thing in Part I. of this strategy, identifying the emerging forest-based industries, products and production technologies which show high growth potential and which are based on BC's comparative advantages.

Singapore's experience shows that a cooperative private-public sector initiative can do very well *what firms must attempt in any case*: predict profitable lines for the next generation of product and process technologies in which firms need to invest now.

Quebec presently gives a five year tax holiday on income, capital and payroll taxes for new small-to-medium enterprises which engage in a business in one of their Information Technology Development Centres, and a two year capital tax holiday on any new investments in manufacturing, computer hardware and buildings used for manufacturing or tourism. Also as of July l999, any new businesses with less than $2 million in paid-up capital are exempt from the provincial capital tax.

BC already has a two year corporate income tax holiday in place for eligible small businesses incorporated between May l, l998 and April l, 200l, and a two year corporate capital tax holiday on eligible BC investment expenditures such as exploration and research.

We therefore recommend a five year corporate tax holiday on Canadian-controlled corporations cultivating or manufacturing pharmaceuticals, nutraceuticals and other natural health products or ingredients from BC wildlands sources; producers of antiphytovirals, mycomedicinals, wild food mushrooms, and essential oils from the same sources and all nature tourism operations. This incentive should also be extended to the six or seven companies which provide technical services to these sectors.

If this notion of a tax holiday on selected industries is not amenable to provincial policy makers, we recommend that the following combination of incentives be granted to these industries:

(l) an export incentive which will grant a 90% tax exemption on all profits above a specified base which results from export sales of the industries named above. This incentive should be granted for three or five years with the longer period being given to companies which do not qualify for:

(2) a pioneer status incentive, which should allow for tax exemptions of 40% of a CCPC's corporate income tax for five years if they undertake new manufacturing activities in BC. Most

of the existing acceptable language of taxation policy was written in a smokestack context and it must be understood that "manufacturing" also includes enhanced growing techniques prevalent in agroforestry operations such as cultivation forests.

Revenue Impacts[1]

The first order impacts on governmental revenues of any proposed tax changes are those which assume no growth of economic activity resulting from the tax changes, and no changes in resulting investment behaviour. They thus overestimate government revenue losses. We have estimated that all the taxation changes proposed above plus the *traditional knowledge fund* proposed in the next section would cost the provincial government approximately $94 million annually in deferred tax revenues. However with a five year perspective which factors in the incentives' sunset features and projected industrial growth, the government is a net tax beneficiary. Experience in Ireland and the Asian economies has shown that sometimes lowering or eliminating taxes on new industries can result in increased tax revenues to the government from the resultant economic growth.

Securing Aboriginal Rights to Traditional Knowledge[2]

To create a stable and confident business climate for the economic development of these non-timber forest resources, we must also settle with first nations peoples and include them centrally in these developments. This involves dealing in an efficient and fair manner with both land claims and *traditional knowledge.*

Here there are three problems. How should the province deal with commercially-useful traditional knowledge taken in the past? What should be done to ensure that first nations have appropriate control over their (undisclosed) traditional knowledge in the present and financially benefit from its commercializations *when they wish to*? And how can the province help perpetuate a rapidly disappearing body of first nations knowledge about the uses of BC fauna and flora – knowledge which we have seen in Part I is providing the commercial basis for a variety of twenty first century health care products.

It must also be realized that commercialization of (often sacred) traditional knowledge is viewed as abhorrent by some first nations peoples, and it is essential that first nations' inputs and decisions about the uses of these biological resources be incorporated at all stages in what is proposed below. An allowance for variation should be promoted and is a mark of respect for aboriginal peoples.

Bioprospecting, the search for fauna and flora whose genetic and chemical information is providing the basis for medicines, biocides and other products, has mainly been conducted in tropical forests of the world, because of their high density of plants and organisms and the resulting number of secondary chemicals churned out by these plants and organisms to survive. One way to bioprospect, we have

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1 On January l, l999, the provincial government put into place $l50 million in tax reductions including reductions in the small business tax, the corporate capital tax threshold and the tax surcharge on high income earners. An R&D incentive is expected by mid-l999.
2 This section was co-authored by Robert Adamson, Supreme Court of Canada clerk to Justice Sopinka, l994-l995.

seen, is simply to ask indigenous peoples what fauna and flora they use for which illnesses (pesticides, nutraceuticals, etc.) or, if it is available, to seek such information in the works of ethnobotanists, ethnopharmacologists and others who have spent their professional lives studying such matters.

In spite of cheap, mass screening techniques, biotech and other corporations are still deeply interested in the knowledge of indigenous peoples in countries with remaining forests. They have realized that industrial products of commercial value can be made from the traditional knowledge of these peoples. For the most part, local people have received nothing for their knowledge. Devil's Club, now entering a multitude of nutraceutical and medicinal herbal formulae and singles on the North American market, was universally used by BC first nations for upper respiratory infections and many other uses. Although they found it, they will receive nothing. To give another recent example, a British pharmaceutical company teamed up with a group from the University of Illinois at Chicago to search for plant-based anti-inflammatory substances recently in Laos. The Lao Institute of Traditional Medicinal Research and the University of Illinois group each receive l% of royalties from resulting sales, but local people were given a dollar for each plant they pointed to which they used as an anti-inflammatory. Several indigenous groups received a total of fifteen dollars.

At the same time, we have seen that advances in computer-automated screening are making it cheaper to mass screen thousands of natural samples rather than ask local elders what they traditionally used for medicines. *Traditional indigenous knowledge, then, will increasingly provide the basis for new herbal nutraceuticals and herbal dietary products rather than for pharmaceuticals.*

When indigenous knowledge of the uses of fauna and flora is the source or basis for new products, the appropriation of that knowledge must be financially rewarded for the same reasons we are correcting the appropriation of first nations lands through the treaty negotiation process –equity and fairness.

There are big problems, however, in trying to assimilate this issue of ownership of traditional knowledge and its rewards into the context of intellectual property law, as is often tried.

Intellectual property rights (IPRs) are legal mechanisms which were developed to protect industrial and individual inventions for a specified period. IPRs are applicable to knowledge when it can be used to create a distinctive and useful product. The law of intellectual property grants ownership to the specific form, expression, or concept which is embodied in a thing, and not to any overt properties of that thing. What is protected are the words in a book, the ingenuity of some software's source code, or underlying information resulting from analyzing and modifying plant biochemicals which provides a new medicine. Patents, copyright, plant breeders' rights, trademarks, and trade secrets are all used to prevent others from copying or selling a product without approval. To obtain a patent, an invention must be novel and non-obvious and usually the patent holder has an exclusive monopoly over the invention for up to thirty years and on royalties for its use, (although the duration period for patents varies from country to country).

The problems are these:

1) in BC some of the most economically valuable traditional knowledge concerning the medicinal and nutraceutical uses of plants has already passed into the public domain through the publications of ethnobotanists (and hence cannot be patented and is up for grabs);
2) the intellectual property laws pertain to individually or corporately-held inventions, while indigenous peoples' rights pertaining to traditional knowledge are often collectively held;
3) finally, although species and wild habitats cannot be patented, new seed strains, purified compounds, genes, and genetically altered microbes, animals and plants can be patented in most countries. Thus although a wild plant or its raw extract cannot be patented, a purified or recombinant drug, or manufacturing method of using a plant for a drug can be patented. There is an incompatibility, in other words, in the forms and expression of indigenous knowledge with patent criteria and with applicability criteria for other intellectual property tools, which were generally developed to protect commercial inventions. There are many other well-known problems with trying to apply existing intellectual property tools in Canada to traditional knowledge (Mann l997).

Existing legislation in Canada and in many countries then, concerning patents, copyrights, plant breeders' rights, trade secrets and related measures does not adequately protect the collective property rights of first nations peoples in their traditional knowledge of uses of flora and fauna. It does not ensure adequate and fair revenues to them resulting from products which might be based on traditional knowledge, nor does it allow them, through the principle of "prior informed consent" to prevent fauna and flora which they do not wish disturbed, from being taken and used in product formulations.

In poor Asian countries until recently any multinational could come and take any wildlands plant (then thought of as the "common heritage of mankind"), slightly alter its composition, patent it, and even traditional farmers from whom it was "discovered" could be prevented from using it. Such happened with a traditionally used plant, *plano noi*, in Thailand, which a Japanese pharmaceutical company patented as an ulcers medicine. At the same time western governments have generally increased the pressure on the developing countries to sign international agreements such as the Intellectual Property Provisions of the GATT, which still allow companies to basically patent their plants.

However many developing countries have realized that adopting certain international western property conventions is not in their economic and cultural interest, have refused to sign such international conventions and are writing their own legislation which aims to (l) adequately protect the property interests of the source `country from which material is taken; (2) recognize property rights of first nations in traditional knowledge of the uses of fauna and flora; (3) through the use of a stringent system of contracts and licensing for bioprospecting, ensure that first nations receive fair and adequate recompense for products based on traditional knowledge.

But there is a major difference between these Asian countries full of little known flora and fauna and BC, whose first nations' medicinal plants have been extensively named and scrutinized by academics, and whose first nations' knowledge has often passed into the public domain (and is hence not patentable) through book and paper publications. These publications now form the main body of knowledge from which several pharmaceuticals, nutraceuticals, and other emerging natural products discussed in Part I were identified. This body of knowledge which has passed into the public domain includes: the names of many plant, animal and soil species used medicinally and their associated illnesses: preparation, processing and storage of species; knowledge of the composition of formulations; planting, care, and selection criteria; The problem thus becomes fiscal compensation for knowledge appropriated long ago. No province is going to assume liability for this, since it could potentially involve hundreds of millions of dollars.

The Convention on Biological Diversity, which Canada has both signed and ratified, says that governments must ensure that access to biological resources on traditional land is subject to obtaining "prior informed consent" of first nations by bioprospectors and that in the case of commercializations, there must be an "equitable sharing of benefits" with them. The Convention is short on mechanisms for achieving these goals, but even so, it is of limited applicability here because it does not apply to biological resources taken and commercialized in the past.

This being the case, we take the view in this strategy that first nations property rights in their traditional knowledge of the uses of biological resources are inalienable, and that these rights were not extinguished when this knowledge passed into the public domain because prior informed consent was not really given, nor was it realized at the time by either party that such knowledge could eventually provide the bases for economically valuable products. To this extent, appropriated traditional knowledge is similar to pirated computer software. It is thus legitimate for BC first nations to claim both aboriginal title to certain land and its fauna and flora (under the condition of continuous occupancy according to the Supreme Court's criteria in the Delgamuukw (l997) decision) and perhaps some form of title to their traditional knowledge about these resources at the time at which the Crown asserted sovereignty over the land subject to the title. Just as some lands were continuously occupied (possessed), so was traditional medicinal plant knowledge –used, reinvigorated, and expanded on a frequent basis. But even if a claim for title to such knowledge can be made, as we see below, this title will bring no benefits to first nations peoples.

At the same time, there are many other legal avenues for first nations to pursue here without turning to the issue of aboriginal title. These include contract law and breach of oral contract, tort and trespass, contract and the law of unconscionability, etc. First nations, in other words, do not have to achieve aboriginal title to traditional knowledge to "claim" it.

Whether or not aboriginal *title* can be claimed for some forms of traditional knowledge, it is certainly the case that indigenous knowledge of the uses of biological resources and associated gathering and practices is an aboriginal *right* as protected by section 35(1) of the l982 Constitution Act. Aboriginal rights have been elaborated by the Canadian Supreme Court in *R. v. Van der Peet* (l996) 2 SCR 507: "It is precisely those present practices, customs and traditions which can be identified as having continuity with the practices, customs and traditions that existed prior to contact that will be the basis for the identification and definition of Aboriginal rights under s.35(l). Where an Aboriginal community can demonstrate that a particular practice, custom or tradition is integral to its distinctive culture today, and that this practice, custom or tradition has continuity with the practices, customs and traditions of pre-contact times, that a community will have demonstrated that the practice, custom or tradition is an Aboriginal right for the purposes of s.35(l) (at para. 63)." Thus no one would claim that the practices, customs and traditional uses of medicinal fauna and flora, for example, did not exist prior to contact or that present practices did not evolve from these and have continuity with those of pre-contact time.

Aboriginal property rights in traditional knowledge must be eventually harmonized with the provincial and federal legislative regime for intellectual property. (Intellectual property law is largely federal while issues of land ownership and civil rights are largely provincial). *But even if aboriginal rights or title can be asserted legally to traditional plant knowledge taken in the past, once the knowledge is recorded and published, it is gone. Land can be restored. Knowledge cannot. And aboriginal title to appropriated knowledge is an empty concept.*

It is not possible to accurately estimate the value of even medicinal/nutraceutical products which were found through first nations knowledge and commercialized over the past fifteen years or so, much less since the time of contact or of sovereignty.

In BC, if we consider just the recording of the names of first nations medicinal plants and their associated illnesses, *approximately twenty five to thirty percent of the entire knowledge base has passed into the public domain*. This means that most of it is still privately or collectively held by first nations. Beyond its spiritual value to aboriginal peoples, this knowledge base is a commercial resource for the identification of new herbal dietary supplements and nutraceuticals. This knowledge base is evanescing rapidly with the death of the elders.

The province should therefore set up a *traditional knowledge fund*, which would be used to pay modest annual honoraria directly to first nations elders knowledgeable in the medicinal and nutraceutical uses of fauna and flora to continue their regular work. Each band has at least one medicinal steward with such knowledge, well-recognized and identifiable by the community. These people, often impoverished, have difficulty recruiting young first nations apprentices, who have lost interest. This fund should therefore also be used to directly pay first nations apprentices a salary to absorb this knowledge. All of this must be done on a non-disclosure basis, otherwise it will not work. The main objective of this fund is to keep this evolving knowledge base alive and growing. There are l91 bands in BC. Paying each first nation ethnobotanist a modest salary of $20,000 per year and $l0,000 yearly to two apprentices each per band would cost the province roughly $ 7.6 million annually, a trivial investment in perpetuating an economically valuable knowledge resource. Although it is not possible to realistically estimate the potential revenues which will arise from forest substances ethnobotanically identified in BC, we have seen in Part I. that l998 collective worldwide revenues for nutraceuticals are between US $10 billion to US $l2 billion.

At the same time, much can be done to ensure aboriginal control of, and financial recompense from, undisclosed traditional knowledge and given the injunction of ordered business development, it is in the government's interest to try to achieve both of these goals. Thus the provincial government should draft and enact basic access legislation which (l) recognizes first nations as owners of traditional knowledge and practices concerning the uses of fauna and flora on their traditional territories; (2) obligates parties seeking commercially useful traditional knowledge from first nations peoples or bioprospecting directly on traditionally-held territories presently or in the future to contract with appropriate first nations to: fully inform local communities about the project and seek their *prior informed consent*. This informing should include a description of the project's objectives, where it will take place, species sought, quantities to be harvested, duration, nature of product, anticipated markets and sales and related information; (3) share direct fiscal benefits, that is fair and equitable compensation, with first nations when the project results in commercializations. These benefits could take the form of royalties, material transfer fees, contributions to capacity building, and other forms. (Having signed and ratified the l992 Convention on Biological Diversity, Canada is actually obliged to enact such legislation).

We have noted in passing that companies throughout the world are seeking not merely indigenous knowledge but indigenous genes for commercial products Several legislative responses in these countries have forbidden the collection, use, commercialization or patenting of first nations' genes and related body materials. This issue must be recognized but is beyond the scope of this work to analyze.

All bioprospectors should also be obligated to deposit duplicate samples of BC biological resources in a designated *ex-situ* herbarium, and this legislation should exempt the exchange between first nation communities of biological resources or related traditional knowledge or practices. Throughout the world and in other parts of Canada (Scientists Act of the Northwest Territories, l974) there is equivalent established or emerging legislation. If properly modified, some of these legislative frameworks could serve as a model for BC. Progressive BC legislation would ultimately pay off business-wise.

References

Antimicrobial Agents and Chemotherapy (l997) 41:2766-2769.

Axelrood, P. (l996) Molecular characterization of microbial biodiversity in forest soils. FRBC No. 97428-ORE.

Axelrood, P. *et al.* (l996) Douglas-fir root-associated microorganisms with inhibitory activity towards fungal plant pathogens and human bacterial pathogens. *Can. J. Microbiol.* 42:690-700.

Beladi, I. *et al.* (l977) *Ann. NY Acad. Sci.* 284:358.

Bennett, R. (l997) FRBC Project HQ96538, Management of Insects and Diseases in British Columbia Conifer Seed Orchards: Pheromone Identification of the Spruce Seed Moth and the Douglas Fir Pitch Moth. Progress Report for April l996-March l997.

Bennett, R. (l997a) FRBC Project HQ96536-RE, Entopathogenic Nematodes for Suppression of Cone Maggots in White Spruce Seed Orchards. Progress Report for April l997-September l997.

Berch, S. (l996) Nisga'a pine mushroom pilot project. Preliminary investigation of the ecology and productivity of *Tricholoma magnivelare* in the field and the laboratory. Final Report to the Nisga'a Tribal Council and Ministry of Aboriginal Affairs, Victoria.

Berch, S. (l996a) *Tricholoma apium* at the Roberts Creek Study Forest: a scientific review. Report prepared for the Sunshine Coast Forest District, Victoria.

Binkeley, C. (l997) quoted in the Vancouver Sun, December l3.

Blatner, K., and S. Alexander (in preparation) "Recent Price Trends for Non-Timber Forest Products in the Pacific Northwest," Department of Natural Resource Sciences, Washington State University, Pullman, Washington.

Bo, L., and Bau Yun Sun (l980) *Fungi Pharmacopoeia (Sinica)* .Kinoko Co., Oakland, Ca.

Butterwoth, J. and E. Morgan (l968) Isolation of a substance that suppresses feeding in locusts. *J. Chem. Soc., Chem. Commun.* 23-24.

Borman, S. (l993) quoted in Chemical and Engineering News, September.

Byers, A. (l989) Chemical ecology of bark beetles. *Experientia* 45: 271-283.

Cao, R. *et al.* (l986) Treatment of 232 cases of Alopecia areata with *Ganoderma capens*. *J. Beijing Med.Col.* 7:2l7-2l8. From *Abstracts of Chinese Medicine* 1:547.

Carson, J. (l997) FRBC Project No. TO 97266-ORE, Six Month Interim Report for the Period April l, l997-October 31, l997.

Castrillo, J. *et al.* (l986) 3-methylquercetin is a potent and selective inhibitor of poliovirus RNA synthesis. *Virology*152:219-227.

Chang, M., and P Pui Hay But (l987) *Pharmacology and Application of Chinese Materia Medica.* Volume 2, World Scientific, Singapore.

Chatfield Dean & Co. (undated) Research Initiating Coverage of Pharmaprint, Inc., New York.

Chen, W. *et al.* (l995) Antifeedant and growth inhibitory effects of the limonoid toosendanin and *Melia toosendan* extracts on the variegated cutworm, *Peridroma saucia* (Lepidoptera: Noctuidae). *J. Appl. Entomol.* 119:367-370.

De Geus, N. (l995) Botanical Forest Products in British Columbia: An Overview. Integrated Resources Policy Branch, BC Ministry of Forests, Victoria, BC.

Delgamuukw v. the Queen (l997) l53 DLR (4^{th}) l93 SCC.

Ebihara, K. and Y. Minimishima (l984) Protective effect of biological response modifiers on murine eytomegalovirus infection. *J. Virol.* 51: ll7-ll8.

Ebina, T., *et al.* (l987a) Antitumor effect of PSK (1) Interferon inducing activity and intratumoral administration. *Gon to Kagaku Ryoho* 14:1841-1846.Tokyo.

Ebina, T. (l987b) Antitumor effect of PSK. Effector mechanism of antimetastic effect in the double grafted tumor system. *Gon to Kagaku Ryoho* 14:1847-1853. Tokyo.

Economist (l998) May 30.

Ellis, D. and W. Russin (undated) Taxol: the history and science of a plant anticancer compound. Department of Horticulture and Botany, University of Wisconsin, Madison.

FAO (l988) Guidelines on the Registration of Biological Pest Control Age nts. Rome.

Farnsworth, N. *et al.* (l985) Siberian ginseng (*Eleutheroccus senticosus):* Current Status as an Adaptogen. In *Economic and Medicinal Plant Research*, vol. 1. Academic Press, New York.

Feng, R. and M. Isman (l997) Selection for resistance to azadirachtin in the green peach aphid *Myzus persicae*. *Experientia* 5l:831-833.

Fogarty, F. (l999) The North American Pine Mushroom (*Tricholoma magnivelare* (Peck) Redhead): *In vitro* Mycelial Culture, Ectomycorrhizal Synthesis Trials, and Preliminary Shiro Analysis. M.Sc.thesis, University of British Columbia, Vancouver.

Fogarty, F. (l998) "Alternative Forest Products – Inventory and Management Strategies for the Sunshine Coast Forest District." FRBC Project No. PA96542 RE.

Freeman, S. (l997) "An Estimate of Pine Mushroom Productivity in the Nahatlatch Watershed," FRBC Report HQ96174 RE.

French, C. *et al.* (l99l) Flavonoids inhibit infectivity of tobacco mosaic virus. *Canadian Journal of Plant Pathology*, 13(l):1-96.

French, C. and G. Towers (l992) Inhibition of potato virus X (PVX) by flavonoids. *Phytochemistry* **31**: 3017-3020.

Furue, H. (l985) Clinical Evaluations of schizophyllan (SPG) in gastric cancer-randomized controlled studies. *Int. J. Immunopharmacol.* 7:333(23).

Gamiet, S. (l997) Ectomycorrhizal Sporocarps in Old Growth Forests in the Coastal Western Hemlock (CWHvm) Subzone of Seymour Watershed, Vancouver, BC. FRBC Interim Report, FRBC Project No. HQ96469 RE.

Gamiet, S., *et al.* (l998) "An Overview of Pine Mushrooms in the Skeena-Bulkley Region," prepared for the Northwest Institute for Bioregional Studies, Smithers, BC.

Gao, B. and G. Yang (l99l) Effects of *Ganoderma applanatum* on cellular and humoral immunity in normal and sarcoma l80 transplanted mice. *Phythother. Res* 5:l34-l38.

Genetic Engineering News (l997) April l5.

Gillespie , D. *et al.* (l997) Collection and selection of natural enemies of twospotted spider mites for biological control, *J. Entomol. Soc.* British Columbia, 94, December.

Gillespie, D. *et al.* (l998) Biology and Application of *Feltiella acarisuga* (Vallot) (Dilptera: Cecidomyiidae) for Biological Control of Twospotted Spider Mites on Greenhouse Vegetable Crops, PARC technical report, No. l45, September l5.

Gunnar, A. (l998) Technical feasibility study for medicinal and aromatic plants which can be grown in the interior of British Columbia. AG Consulting. A report to the Science Council of British Columbia.

Hallman, R. (l998) Draft Strategic Plan for Agroforestry in British Columbia. Ministry of Agriculture, Fisheries and Food, Creston.

Health Canada (l998) Regulatory Framework for Natural Health Products. final report of the advisory panel on natural health products; a presentation to the House of Commons Standing Committee on Health, Ottawa.

Herbalgram (l997) #41, Fall.

Herbalgram (l998) #42, Spring.

Hobbs, C., (l995) *Medicinal Mushrooms*, Botanica Press, Santa Cruz.

Holm, W. (l998) The Agricultural Land Reserve in the Okanagan: Renewing the Public Policy Prescription. a report submitted to the BC Fruit Growers Association by W.R. Holm and Associates, Bowen Island.

Holm, W. and D. MacGregor (l998) Processing Guide for Specialty Crops. a report published by the Science Council of BC - Okanagan.

Hu, B. and P. But (l987) Chinese materia medica for radiation protection. *Abstracts of Chinese Medicines.* 1:475-490.

Huang, S. *et al.* (l995) *Proceedings of the National Academy of Science* 92:88l8-8822.

Hudson, J. *et al.* (l994) Antiviral assays on phytochemicals; the influence of reactor parameters. *Planta Medica* 60:299-332.

Hudson, J. *et al.* (l994a) *Antiviral Compounds from Plants.* CRC Press, Boca Raton.

Humble, L. (l997) FRBC Project PA965880-RE, Canopy Insect Biodiversity for Silvicultural Systems in Coastal Montane Forests.

Hung-Cheh, C. and K.W. Mieng-Hua (l986) Improved assay for germanium in crude drugs. *J. Taiwan Pharm. Assoc.* 38:189-198. In *Abstracts of Chinese Medicine* l:337

Iizuka, C. *et al.* (l990) Antiviral composition extracts from basidiomycetes. Eur. Pat. Appl. EP 464,311.

Iizuka, C *et al.* (l990a) Extract of basidomycetes from L*entinus edodes* for treatment of human immunodeficiency virus (HIV) Shokin Kogyo Co. Eur. Pat. Appl. EP 370,673.

Isman, M. (l994) Botanical Insecticides and Antifeedants: New Sources and Perspectives. *Pesticide Research Journal,* Vol. 6(l) 11-19.

Isman, M. (l997) Neem and Other Botanical Insecticides: Barriers to Commercialization, *Phytoparasitica* 24: 4, l997.

Isman, M. (unpublished) Biorational Insecticides, Botanical Insecticides and Behavior Modifying Substances: Their Possible Impacts on the Environment.

Ito, H e al (l973) Studies on antitumor activity of basidiomycete polysaccharides. Antitumor effect of fungal and bacterial polysaccharides on mouse tumors. *Mie. Med. J.* 23:ll7-l27.

JAMA (l998) cited in the Wall Street Journal, November 11.

James, D. *et al.* (l996) Combination of chemotherapy and *in vitro* culture for the elimination of a fruit tree virus and the development of an immuocapture RT-PCR protocol for rapid sensitive screening. *Proceedings of the Canadian Society of Plant Physiologists* 38(2): l3.

James, D. *et al.* (l997) Elimination of apple stem grooving virus by chemotherapy and development of an immunocapture RT-PCR for rapid sensitive screening. *Ann. Appl.Biol.* 131:459-470.

Kakumu, S *et al.* (l99l) Effects of schizophyllan, a polysaccharide on interferon Gama antibody production and lymphocyte proliferation specific for hepatitus B virus antigen in patients with chronic hepatitus B. *Int. J. Immunopharmacol.* 13:969-975.

Kandefer-Szerszen, M. *et al.* (l979) Fungal nucleic acids as interferon inducers. *Acta Microbiol. Pol.* 28:277-291.

Kasamatsu, T. (l982) The radiation of sensitizing effect of PSK in the treatment for cervical cancer patients. From Yamamura, Y. *et al.* (eds.) *Immunomodulation by MicrobialProducts and Related Synthetic Compounds.* pp 463-466, Amsterdam.

Keung, W. *et al.* (l995) *Proceedings of the National Academy of Science* 92:8990-8993.

Kobaisy, M. *et al.* (l997) Antimycobacterial polyynes of Devil's Club (*Oplopanax horridus*), a North American native medicinal plant. *J .Nat. Prods.* 60:1210-1213.

Komatsu, N. *et al.* (l969) Host mediated antitumor action of schizophyllan, a glucan produced by *Schizophylum Commune. Gann.*60:137-144.

Komatsu, N. *et al.* (l973) Protective effects of schizophyllan on bacterial infections of mice. *Jpn. J. Antibiot.* 26:283.

KPMG (l997) KPMG Biotechnology Report, Winter.

KPMG (l999) Canadian Tax Letter at http://www.kpmg.ca

Kubo, I. and K. Nakanishi (l979) Some terpenoid insect antifeedants from tropical plants, pp. 284-294. In Advances in Pesticide Science, Vol. 2, H. Geissbuehler (ed.) Pergamon Press, Oxford.

Ladani, A. *et al.* (l993) Effect of lentinan on macrophage cytotoxicity against metastic tumor cells. *Cancer Immunol. Immunother.* 36;123-126.

Lipsett, M. (l997) Cashing in on Federal Innovation Incentives for Research and Development: a Province by Province Scorecard. Paper prepared for the Tax Executives Institute BC Provincial Liaison Meeting, 28 May, l997.

Locke, S. and M. Hornig-Rohan (l983) *Mind and Immunity: Behavioral Immunology: An Annotated Bibliography l976-l983.* Institute for the Advancement of Health, New York.

Malhotra, B. *et al.* (l996) Inhibition of tomato ringspot virus by flavonoids. *Phytochemistry* 43(6): 1271-1276.

Mann, H. (l997) Intellectual Property Rights, Biodiversity and Indigenous Knowledge: A Critical Analysis of the Canadian Context. Submitted to the Canadian Working Group on Articles 8(j) of the Convention on Biological Diversity. Ottawa.

Marco, J. and O. Barbera (l990) Natural Products from *Artemisia* L. in Rahman, A. (ed.) *Studies in Natural Product Chemistry,* Vol. 7, Elsevier Science Publishing, Amsterdam.

Matsuura, H. *et al.* (l995a) Antibacterial and antifungal compounds from *Glehnia littoralis* F. Schmidt. submitted to *Phytochemistry.*

Matsuura, H. *et al.* (l995b) Antibacterial compounds from *Ceanothus velutinus* Dougl. Submitted to *Phytochemistry.*

Matsuura, H. *et al.* (l995c) Antimicrobial constituents of *Empetrum nigrum* L. submitted to *Planta Medica.*

Matsuura, H. *et al.* (l995d) Antibacterial constituents of *Geum macrophyllum* Willd. (unpublished manuscript).

Matsuura, H. *et al.* (l996) Antibacterial and antifungal polyine compounds from *Glehnia littoralis* spp. *leiocarpa. Planta Medica* 62:259-259.

Matsurra, H. *et al.* (l996a) An antibacterial thiophene from *Balsamorhiza sagittata. Planta Medica* 62:655-66.

McCutcheon, A. *et al.* (l992) Antibiotic screening of medicinal plants of the British Columbian native peoples. *J. Ethnopharmacology* 37:213-223.

McCutcheon, A. *et al.* (l996) Ethnopharmacology of Western North American Plants With Special Focus on the Genus *Artemisia L.* Ph.D. dissertation, Department of Botany, UBC, Vancouver.

McCutcheon, A. *et al.* (l997) Anti-mycobacterial screening of British Columbian Medicinal Plants. *Int. J. Pharmacognosy* 35:1-7.

Misaki, A. *et al.* (l98l) Studies on the interrelation of structure and antitumor effects of polysaccharides:: Antitumor action of periodate-modified, branched (1-3-beta-Glucan) of *Auricularia auricula-judae,* and other polysaccharides containing (1-3)-Glycosidic Kikurages. *Carbohyd. Res.* 92:115-129.

Mitomo, K. *et al.* (l980) Health food material from *Coriolus versicolor*. Japanese patent application A61K35/84.

Mizuno, T. (l995) Shitake. *Lentinus edodes:* functional properties for medicinal and food purpose. *Food Reviews International.* 11(1): lll-l28.

Mizuno, T. *et al.* (l995) Health foods and medicinal usages of mushrooms. *Food Reviews International.* 11(1): 69-81.

Ohmori, T. *et al.* (l989) The correlation between molecular weight and antitumor activity of galactosaminoglycan (CO-N) from *Cordyceps ophioglossoides. Chem. Pharm. Bull.* 37:1337-1340.

Ohmoni, T. et al (l989a) Isolation of galactosaminoglycan noiey (CO-N) from protein-bound polysaccharide of *Cordyceps ophioglossoides* and its effects against murine tumors. *Chem. Pharm. Bull.* 37:1019-1022.

Ohsawa, T. *et al.* (l992) Studies on constituents of fruit body of *Polyporus umbellatus* and their cytotoxic activity. *Chem. Pharm. Bull.* 40:143-147.

Oka, T. *et al.* (l985) Antitumor effects and augmentation of cellular immunity by schizophylan and bestatin. *Okayama Igakkai Zasshi* 97:527-541.

Okamura, K. *et al.* (l989) Adjuvant immunochemotherapy: Two randomized controlled studies of patients with cervical cancer *Biomed. Pharmacother.* 43:177-181.

Piltz, D. and R. Molina (l996) (eds.) Managing Forest Ecosystems to Conserve Fungus Diversity and Sustain Wild Mushroom Harvests. General Technical Report PNW-GTR-37l, Pacific Northwest Research Station, Portland.

Price Waterhouse (l997) Quoted in the Vancouver Sun, December l3.

Quiring, D. and J. Sweeney (l997) SCBC Project No. FR 96/97-873).

Reynolds, J. (l993) *Martindale, The Extra Pharmacopoeia,* 30th edition. The Pharmaceutical Press, London.

Saxena, G. *et al.* (l994) Antimicrobial constituents of *Rhus glabra* L. *Journal of Ethopharmacology* 42:95-99.

Saxena, G. *et al.* (l995a) Antimicrobial compounds from *Alnus Rubra* Bong. *Int. J. .Pharmacognosy* 33 (1):33-36.

Saxena, G. *et al.* (l995b) Antimicrobial compounds from *Moneses uniflora* (L.) A. Gray. Submitted to *Phytochemistry.*

Saxena, G. *et al.* (l995c) Antimicrobial constituents of *Ipomopsis agreggata* (Push) Spreng. Submitted to *Phytochemistry.*

Saxena, G. *et al.* (l995d) Antimicrobial constituents of *Oplopanax horridus.* (unpublished manuscript).

Saxena, G. *et al.* (l996) Chlorochimaphillin: a new antibiotic from *Moneses uniflora. J. Nat. Prod.* 59:62-65.

Schroder Securities Ltd. UK (undated) internal company document.

Scientists Act (l974) R.S.N.W.T. c. S-4.

Shamoun, S. *et al.* (l997) FRBC Project No. HQ 96244-RE, Interim Report of the Period June l, l997-December l, l997.

Sheng, J. and Q. Chen (l987) Anticoagulant effect of polysaccharides from *Auricularia auricula, Tremella fuciformis,* and *Tremella fuciformis* spores. *Zbongguo Yaoke Daxue Xuebao* 20:344-347.

Stock, A. (l98l) The western balsam bark beetle, *Dryocoetes confusus:* secondary attraction and biological notes. M.Sc. Thesis. Simon Fraser University, Burnaby, BC.

Su, C. *et al.* (l993) Hepato-protective triterpenoids from *Ganoderma tsugae.* Proceeding of the First International Conference on Mushroom Biology and Mushroom Products, August, l993. in Chang, S. *et al.* (eds.) *Mushroom Biology and Mushroom Products,* Chinese University Press, Hong Kong.

Tabata, K. *et al.* (l98l) Ultrasonic degradation of Schizophyllan, an antitumor polysaccharide produced by *Schizophyllum commune* Fires. *Carbohyd. Res* 89:121-135.

Towers, G. *et al.* (in press) Antimicrobial activities of phytochemicals from British Columbian medicinal plants. In K. Hostettmann et al. (eds.) *Chemistry, Biological and Pharmacological Properties of Medicinal Plants from the Americas*. Harwood Academic Publishers, Switzerland.

Tsukagoshi, S. *et al.* (l984) Krestin *Cancer Treatment Reviews* 11:131-155.

Turner, N. (l974) *Plant Taxonomy and Systematics of Three Contemporary Indian Groups of the Pacific Northwest.* Ph.D. thesis, University of British Columbia, Vancouver.
Turner, N. *et al.* (l980) *Ethnobotany of the Okanagan-Colville Indians of British Columbia and Washington.* BC Provincial Museum Occasional Paper No 21, Victoria.

Turner, N. *et al.* (l990) *Thompson Ethnobotany: Knowledge and Usage of Plants by the Thompson Indians.* BC Provincial Museum Memoir No 25, Victoria.

Valisolalao, J. *et al.* (l983) Steroides cytotoxiques de *Polyporus versicolor. Tetrahedron* 39:2779-2785.

Vitens, G. (l998) Overview of the Health Food Supplement and Medicinal Herb Processing and Brokerage Industries of British Columbia. Report to the BC Ministry of Agriculture and Food. Victoria.

Yongshhou, X. *et al.* (l993) Diterpene resin acids: major active principles in tall oil against variegated cutworm, *Peridroma saucia* (Lepidoptera: Noctuidae). *Journal of Chemical Ecology,* Vol. 19, No. 6.

Wang, G. *et al.* Antitumor active polysaccharides from the Chinese mushroom Songshan lingzhi, the fruiting body of *Ganoderma tsugae. Bioscience, Biotechnology and Biochemistry* 57:894-900.

Wang, Y. (l995) *Tricholoma matsutake.* Ph.D. thesis, University of Otago, Dunedin, New Zealand. Three volumes.

Wang, Y. *et al.* (in preparation) Morphology and Anatomy of Infections of *Tricholoma matsutake* and Related Species.

Waterworth, H.E. and A. Haddi (l998) Economic losses due to plant viruses. in Plant Virus Disease Control, Hadidi et al. (eds.) American Phytopathological Society Press, St. Paul, Minn.

Weigand, J. (l997) Forest management for the North American pine mushroom (*Tricholoma magnivelare* (Peck) Redhead) in the Southern Cascade range. Unpublished Ph.D. dissertation, Oregon State University (Corvallis).

Westland Resource Group (l998) “Botanical Forest Products Effects Upon Operational Planning,” report prepared for the Forest Practices Branch, Victoria, BC.

Won, S. *et al.* (l992) *Ganoderma tsugae* mycelium enhances splenic natural killer cell activity and serum interferon production in mice. *Jpn. J. Pharmacol.* 59:171-176.

Xia, E. and Q. Chen (1989) Biological activities of polysaccharide from *Auricularia auricula, Zbongguo Yaoke Daxue Xuebao,* 20:227-230.

Xia, E. *et al.* (l987) Effect of polysaccharides from *Auricularia auricula*, *Tremella fuciformis* and *Tremella fuciforus* spores on DNA and RNA biosynthesis by lyphocytes. *Zbongguo Yaoke Daxue Xuebao* 18:14143.

Xue, W. *et al.* (l989) Prevention and treatment of alloxan-induced diabetes in mice by polysaccharides isolated from *Tremella fuciformis* and *Auricularia auricula. Zbongguo Yaoke Daxue Xuebao* 20:181-183.

Yamada, H. *et al.* (l984) Structure and antitumor activity of an alkali-soluble polysaccharide from *Cordyceps ophioglossoides. Carbohydr. Res.* 125:107-115.

Yamamoto, T. *et al.* (l981) Inhibition of pulmonary metastasis of Lewis lung carcinoma by a glucan, schizophyllan. *Invasion Metastasis* 1:71-84.

Yan, Y. *et al.* (l985) Anticarcinogenic effect of the polysaccharide from Laoshan *Polystictus versicolor*. *Medical Journal of Chinese People's Liberation Army* 88:380-383. From *Abstracts of Chinese Medicine* 2:188.

Yang, Q., and S. Jong (l989) Medical mushrooms in China. in Proceedings of the Twelfth International Conference on the Science and Cultivation of Edible Fungi, XII:631-643.

Yang, Q. *et al.* (l993) A new biological response modifier - PSP. in *Mushroom Biology and Mushroom Products,* S. Chang (ed.), The Chinese University Press, Hong Kong.

Ying, J. *et al.* (l987) *Icones of Medicinal Fungi from China.* Science Press, Beijing.

Yoneda, K. *et al.* (l991) Immunoregulatory effects of sizofiran (SPG) on lymphocytes and polymorphonuclear leukocytes. *Clin. Exp. Immunol.*86:229-235.

Zhang, G. and Y. Li (l987) Determination of nucleosides and nucleotides in *Cordyceps sinensis. Chinese Journal of Pharmaceutical Analysis* 7:6-9. in *Abstracts of Chinese Medicine* 2:142.

Zhang, L. *et al.* (l993) Effects of ling zhi on the production of interleukin-2 (IL-2). In *Research on Ganoderma lucidum,* Shanghai Medical University Press, Shanghai.

Zhang, S. *et al.* (l985) Activation of murine peritoneal macrophage by the natural Cordyceps and the cultured mycelia of *Cordyceps sinensis. Chinese Journal of Integrated Traditional and Western*

Medicine 5:45-47. In *Abstracts of Chinese Medicine* 1:570.

Zhou, H. *et al*. (l989) Antihepatitis and antimutation effect of polysaccharide from *Tremella fuciformis* and *Auricularia auricula. Zbongguo Yaoke Duxue Xuebao* 20:51-53.

Zhu, D. (l987) Recent advances on the active components of Chinese medicines. *Abstracts of Chinese Medicines* 1:251-286.