INDUSTRIAL UTILIZATION OF MEDICINAL AND AROMATIC PLANTS

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Abstract

A tremendous change has been going on globally in the last two decades, and especially in the last one in favour of the increased use of medicinal and aromatic plant products in pharmaceutical and related industries. This interest needs a closer focus in order to analyze the reasons behind this positive trend. Therefore, the paper is divided into two parts. The first part mainly deals with medicinal plants and focuses on the facts behind this sudden but steady upsurge of interest in industrial utilization of medicinal plant products as reflected by the growing market figures worldwide. In the final part, the world situation as regards aromatic plants is covered. Essential oils, aromatic plant extracts and aromachemicals are dealt with from the perspective of industrial utilization.

1. Introduction

It is estimated that there exists on earth, up to 750.000 flowering or seed bearing plants, although the number of already registered plants is around 300.000. It is also estimated that the number of medicinal plants vary between 30.000 to 75.000, although, WHO has compiled a list which contains ca. 20.000 medicinal plants used all over the world. It has also been stated that about 4000 plant drugs have been widely used and that in Western Europe about 400 plant drugs are widely traded. These figures imply that medicinal plants in the world can be regarded as rare, although, one should also take into consideration the fact that only about 20% of all the registered plant species have, so far, been more or less, investigated. 99% of the plants of the Amazonian basin in South America have not, reportedly, been investigated scientifically.

2. Medicinal Plants

A WHO study has shown that 80% of the world population are dependent on plant based medicaments. With their significance so highly esteemed by the majority of the world population, one should do more about their exploitation, and folklore claims on some plants for miraculous cures should not be ridiculed off-hand.

Luckily, in the last two decades the situation has changed dramatically. A revival of interest in developed countries on plant based medicines has forced these countries to seriously reconsider legislations governing the use of plant drugs and plant based medicaments.

2.1. Legislative Changes

In Japan, 147 Kampoh medicines, meaning traditional medicines, became eligible for reimbursement by the national insurance scheme in 1976. Based on the assumption that their safety and efficacy have been established through their centuries long use, no

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clinical validation was thought necessary for these medicines to attain prescription status (Steinhoff, 1996).

In Germany, German Federal Health Agency established an expert committee called "Commission E" to evaluate the safety of herbal or phyto medicines. The committee, by 1994 had issued 433 monographs on plant drugs and combinations with ca. 200 approved herbs. These monographs have been published in the German Official Gazette. The monographs have, since then, been used to facilitate the assessment of marketing applications for herbal products. They contain description of the products and their contents, their pharmacological properties, accepted indications, contra-indications, adverse effects, interactions with other drugs, dosage, quality requirements and recommended storage conditions.

In August 1994, the 5th Amendment of the German Drug Law came into force. This amendment has established a simplified procedure for registration of herbal medicines, taking traditional use as a proof of efficacy for certain category of products. In accordance with the law the German Federal Health Agency has compiled lists stating which preparations with prophylactic and therapeutic indications allowed to make reference to a traditional use as proof of efficacy (Steinhoff 1996, Zhang 1996, Keller 1996).

In France, the Ministry of Health published a guideline in 1987 to give a better defined status to plant based drugs and draw up a positive list of plant drugs for registration via an abridged dossier. Historical proof of the long-term widespread traditional use and their well established use in self medication were taken into account for establishing safety with an optimum benefit to risk ratio.

In 1990, the guideline was completed to include clauses on marketing authorization for new products and validation of products already in the market. This guideline includes a list of 174 plants or plant parts with defined therapeutic indications, and a list of 35 accepted therapeutic indications for minor ailments. Moreover, a list of fixed combinations of plants was given for laxative herbs. The guideline also includes a list of toxicological recommendations and rules for labeling and packaging of herbal medicines (Steinhoff 1996, Zhang 1996, Keller 1996).

In the USA, Dietary Supplement Health and Education Act became effective in 1994. This act defines herbs, which have been shown to be useful in preventing chronic diseases, as dietary supplements. They are considered as food and sold in dosage forms such as tablets, capsules, liquids, etc. Such products do not require a premarket approval by the Food and Drug Administration (FDA). No medical claims can be indicated, however, changes in the structure and function of the human body by phytomedicines can be mentioned in advertisements and on product labels. The FDA now allows statements of nutritional support, in other words structure and function claims, provided they are based on clinical evidence in the company's own files. This law is seen as an important step for the full recognition of herbal medicines in the USA. At present, there is no distinction between a conventional medicine and a herbal medicine. The same stringent rules apply for the registration of both. The FDA does not accept bibliographic data on a therapeutic use, clinical proof is required as evidence for efficacy (Steinhoff 1996, Zhang 1996, Keller 1996, Griggs 1997).

However, the American public is forcing the authorities to soften the hardline attitude currently in place. National Institute of Health (NIH) opened an office of alternative medicine in 1993 and now, 34 out of 125 medical schools in USA offer courses in alternative medicine (Griggs 1997).

In China, where there is a strong tradition of herbal medicine, different rules than those for conventional medicines apply for the clinical evaluation of herbal medicines. The rules were revised in 1992 to further facilitate the evaluation of herbal medicines. If traditional chinese medicinal materials are used in the formulation of a pharmaceutical,

pharmacological and toxicological data are not requested by the authorities, provided the pharmaceutical meets certain criteria, such as it does not contain any toxic material, the drugs are included in the pharmacopoeia, and the traditional manufacturing process is carried out in its manufacturing efficacy (Steinhoff 1996, Zhang 1996).

The European Community Directive 65/65 clearly defines that herbal remedies are medicinal products, and the European Court of Justice endorsed this interpretation in 1995. According to this directive, as well as the following directives 75/318 and 319, and 91/507, published literature must be considered in the case of well-known medicinal products which largely embrace herbal medicinal products, and it is not necessary to repeat all the tests and clinical trials, if publications give sufficient evidence that the product in question has a well established medicinal use with recognized efficacy and acceptable level of safety. Phytomedicine manufacturers in Europe have one of the two options. They can either conduct clinical trials on their products and market them as phytomedicines, or they can market them in the newly created category with labels that make no specific claims but state only "traditionally used in the treatment of" (Keller 1996, Griggs 1997, Grünwald *et al.* 1996).

Since 1995, besides national regulations for registration in each member state, a decentralized registration procedure has become effective in the European Union. According to this new procedure, if a drug is registered in one EU member state, the holder of registration can apply for mutual recognition in other member states. If no compromise is reached within 90 days, the central EU agency, CPMP (Committee for Proprietary Medicinal Products) has to find a solution which is binding for all the EU states (Steinhoff 1996, Keller 1996, Grünwald *et al.* 1996).

In Europe, each herbal extract is legally recognized as one active constituent in assessing the efficacy (Keller 1996). Standardized extracts with a reproducible therapeutic activity can be formulated into medicines. Well known examples are extracts of senna, St.John's wort, Ginkgo biloba, garlic, etc.

In case of fixed combinations, the regulatory situation is a little more complicated in Europe, multi-drug combinations are defended on the grounds of synergistic effect. If this is true, it has to be proven. The composition of such herbal combinations and the contribution of each ingredient to the activity must be clearly indicated. Benefit to risk ratio must be well balanced and compared to those of single ingredients. The applicant has to impress the regulatory authorities for his product to get marketing authorization (Keller 1996).

Recent years have witnessed an increase in the number of plant drugs in pharmacopoeias, and standards. In the European Pharmacopoeia, 60 herbal monographs have been published and over 45 draft monographs are under review. ESCOP (European Scientific Cooperative on Phytotherapy) published 50 monographs on plant drugs by 1997 (Blumenthal 1997) and 30 are under review (Griggs 1997). Such monographs are rephrased by CPMP (Committee on Proprietary Medicinal Products) of the European Union as Summary of Product Characteristics, or SPCs. In 1994, CPMP published a document entitled "Coordinated Review of Monographs of Herbal Remedies" and adopted final core-SPCs for four laxatives (Zhang 1996, Keller 1996). World Health Organization (WHO) has been preparing a long list of monographs on medicinal plants to establish international specifications for the most widely used medicinal plants. 28 monographs are expected to be published soon.26 more monographs are being prepared (Zhang 1996, Blumenthal 1997). The latest edition of the Chinese Pharmacopoeia contains a list of 647 crude drugs of plant origin together with their formulations, methods of preparation, quality control and purity tests and related information. 1996 edition of British Herbal Pharmacopoeia has 169 monographs on plant drugs (Blumenthal 1997).

All these trends have resulted in a wider and safer use of phytomedicines especially in Europe, and the phytopharmaceutical industry has been manufacturing registered phytomedicines in accordance with GMP (Good Manufacturing Practice) regulations.

An important development in early 1980s has been the reintroduction of phytotherapy education in the curricula of the Faculties of Medicine in Germany. This has resulted in German physicians to prescribe registered herbal medicines and the industry was not slow in responding to comply with this changing trend. In 1991, an inquiry made in the member states of the European Community showed that about 1400 herbal drugs were in use. Now, in Germany more than 80% of all physicians regularly prescribe herbal medicines (Griggs 1997, Grünwald *et al.* 1996).

Another important reason for the strong market position of phytomedicines in Europe is the fact that phytomedicines are included in reimbursement schemes. In Germany and France approximately 40% of all herbal remedies are reimbursed, although in UK, USA and Canada only plant based laxatives are partially reimbursed (Grünwald *et al.* 1996).

2.2. Worldwide Sales of Phytopharmaceuticals

The worldwide retail sales of phytomedicines amounted to US$ 12.4 billion according to 1994 figures. Europe leads the market with an impressive sales volume of 6.5 billion dollars*. The share of European Union member states is 6 billion dollars. Europe is followed by East Asian Countries (US$ 2.3 billion), Japan (US$ 2.1 billion) and North America (US$ 1.5 billion). The growth rate of the market is estimated as 8% in the European Union, 12% each in North America, Other European countries and South-East Asia, and 15% in Japan and 15% in India and Pakistan (Grünwald *et al.* 1996).

In Europe, Germany holds the biggest share with US$ 2.5 billion, followed by France with US$1.6 billion and Italy with US$ 600 million. Every citizen in the European Union spends US$ 17.4 per year for herbal medicines.

In 1994, consumer surveys in Europe clearly showed the growing positive public attitudes to complementary medicine. 60% of both the Dutch and Belgians were ready to pay extra health insurance premiums for it and were in favour of it being included in the National Health System. Public opinion in the UK was 74% in favour of its inclusion in the National Health Insurance scheme (Zhang 1996).

In 1993, 57% increase in the purchase of herbal medicines was reported in UK. UK is one of the fastest growing markets in herbal products. At least £1 million per annum of National Health Service (NHS) funds is spent on alternative medicine. The Health Product Market was worth £800 million (=$1.3 billion) in the UK in 1995. Of this 48% is from non-food supplements, herbal remedies and complementary medicines. The trade has increased at over 6% per annum from 1991 to 1995 (Griggs 1997, Runham 1996).

In USA, each year about 125 million prescriptions which contain a pharmaceutical derived from a higher plant are written. OTC sales of herbal medicines was estimated to be worth US$11 billion a year in USA. This figure obviously includes combination of herbal products with synthetics or minerals, and vitamins as well. Herbal remedies market in USA is estimated at US$ 3.24 billion a year (Johnson 1997).

One in three American adults has been reported to use herbal remedies and spend US$ 54 per year to treat more common health conditions like colds, burns, headaches, allergies, insomnia, etc. (Johnson 1997).

According to a survey conducted in 1996 on sales of herbs in US health food stores, the following five drugs topped the list with 33%: Echinacea (9.6%), garlic (7.2%), ginseng (6.4%), ginkgo (5.1%) and hydrastis (4.7%) (Anon. 1997). Herbal extracts market in USA was US$ 320 million in 1996 and is estimated to reach US$ 650 million in 2001 with an annual growth of 15.2% (Lehner 1997).

The non-prescription drugs market in 1996 was worth an estimated US$ 49 billion worldwide. With 31% share, North America is leading the OTC market, followed by western Europe at 26%, Japan at 16%, South East Asia at 11%, Latin America at 5%, Central and Eastern Europe at 4% and the rest of the world at 7% of the global OTC market based on 1995 figures (Miceli 1997).

In Japan, between 1974 and 1989, a 15-fold increase was observed in herbal product sales compared to only less than 3-fold increase in the sales of other pharmaceutical products (Zhang 1996).

In China, about one billion people making up of over 85% of the total population use plant-based medicines. They are used by almost half the population in urban centres and over 90% in rural areas for primary health care (Srivastava *et al.* 1996, Lambert *et al.* 1997).

Each year, 460.000 tons of plant materials are required to produce factory-made plant based medicines in China. The sale of crude plant drugs was estimated at US$ 1.1 billion in 1993. Some 200 medicinal plants are cultivated in 440.000 hectares with a yield per annum of over 300.000 tons. More than 700 farms are engaged in cultivating high-quality medicinal plants. According to a nationwide survey conducted in early 1990s, 7295 medicinal and aromatic plants are used in traditional medicine in China. They are variously used as raw materials (Lambert *et al.* 1997, Xiao *et al* 1994). In 1990, 700.000 tons of plant materials were reportedly used by Chinese doctors in traditional prescriptions. Traditional medicines have a 40% share in the pharmaceuticals market in China. The sales of traditional medicines in China have increased 113% over the last five years. There are over 5000 licensed patent medicines, including 2500 health products that utilize 11.559 natural products (Lambert *et al.* 1997). In 1993, the total sales of herbal medicines amounted to more than US$ 2.5 billion. In addition, US$ 400 million worth of herbal medicines were exported (Zhang 1996).

In South-East Asia, at least 800 million people are estimated to rely on herbal remedies. This is largely due to the dominance of traditional Chinese medicine and local traditions in those countries and also to the weak availability of conventional medicines. The official recognition of traditional systems of medicine is certainly a factor for their widespread use, such as in India and China. Conventional medicines produced in India are estimated to meet only 30% of the annual demand, traditional systems of medicine such as Ayurveda, Unani, Siddha and to some extent Tibetan have a share of 70% of the formal medicine market which corresponds to 600 million people.

Of about 25.000 vascular plants growing in the Indian subcontinent, the half consist of endemic plants and 7000 medicinal plants are used in traditional medicine systems in India. Exports of crude drugs and essential oils in 1994-95 from India were US$ 53 million and US$ 13 million, respectively, altogether bringing a total revenue of US$ 66 million. These are formal figures. There is no estimation on the value of the informal market. Currently there are 460.000 traditional medicine practitioners in India, and 215 hospitals and 14.000 dispensaries are devoted to traditional medicine. About 540 important medicinal plants are used in traditional formulations. Of the 2000 drug items recorded in the Indian Materia Medica, 1800 are of plant origin and 80% of the raw materials used in the manufacture of drugs are forest products (Lambert *et al.* 1997).

In Western Europe, medicinal and aromatic plants are grown in 70.000 hectares. Spain is the largest producer of herbs in the European Union with 28.000 ha. France is the second largest European producer with 23.000 ha. In France, some 400 ha are harvested from wild plants. France imports 60% of its medicinal herb requirement while it is 90% in Germany and UK (Runham 1996).

2.3. Biodiversity Prospecting

Biodiversity Prospecting is a relatively new term to describe collection, screening and commercialization of natural products. As it is generally used by workers of biodiversity conservation, it has also been described as "the exploitation of biodiversity for commercially valuable genetic and biochemical resources" (Laird 1995). It refers to biological resources, which may come from plants, insects, fungi, bacteria or marine organisms. Such materials are generally supplied for research purposes to pharmaceutical and agricultural industries. While the pharmaceutical companies conduct research into discovering new chemical leads, the agricultural industries seek out new genes for breeding programmes or genetic engineering (Baker *et al.* 1995).

Many big or smaller pharmaceutical companies are more and more investing in research into medicinal and aromatic plants, because they see it as a promising and prospective field.

In recent years, several pharmaceutical companies have launched large scale screening programmes for natural products, mainly plants. Materials are generally collected in developing countries. Most of which are located in the tropical belt where a rich biodiversity exists. Collection is either realized by contracted individuals, companies, institutes, local communities or national governments. According to the Convention on Biological Diversity (CBD), biodiversity prospecting should be carried out in such a way to conserve biodiversity, encourage sustainable utilization and develop technical skills. Source countries are claiming national sovereignty over their country's genetic and biological resources based on the CBD (Baker *et al.* 1995).

As development of a new drug or a new commercial product is a lengthy business, it may take years to come up with a marketable product and the source country can only benefit when it ever occurs. Merck has signed a multimillion dollar agreement with the Costa Rica's National Institute of Biodiversity (INBio) to collect about 1000 plant, insect and soil samples for screening purposes. Merck has also promised to contribute to the setting up of an extraction laboratory for INBio in Costa Rica. The agreement requires Merck to pay an agreed amount of royalties to INBio on any drug developed. Merck markets several drugs with natural product origin including Mevacor, Primaxin, Mefoxin and Ivermectin (Griggs 1997, Laird 1995, Baker *et al.* 1995, Scimone 1997).

R&D through biodiversity prospecting is generally carried out by the pharmaceutical industry in industrialized countries with huge budgets. This industry spends over US$ 200 million to develop a pharmaceutical with new molecular entities (NMEs) isolated from plants (Scimone 1997). While the pharmaceutical industry focuses on single components, traditional or international herbal medicine rely on standardised extracts from a single or a combination of plants.

In most biodiversity-rich countries, traditional medicine is practiced by a sizeable population. Due to scarcity of financial resources, indigenous knowledge and plant resources are relied on to solve national health problems. A WHO study has, therefore, shown that for 80% of the world's population, phytomedicine is the only provider of health.

2.4. Worldwide Sales of Pharmaceuticals

The worldwide sale of pharmaceuticals in 1996 was $222 billion (Scimone 1997). According to a study published in 1990, the developed countries produced 73% and consumed 72% of the world production. Merck in USA alone made a revenue of $7.7 billion in 1990. This amount exceeded the entire pharmaceuticals production of Latin America, that year (Ballance *et al.* 1992).

The developing countries + eastern block countries had a world production share of 27% and consumed 28% of the world pharmaceuticals in 1990. Eastern block countries' share in world production was 8.6%.

China produced 3.55% and consumed 3.58% of the world pharmaceuticals production in the same year, while India produced 1.29% and consumed 1.25%. These two countries realized 4.84% production and 4.87% consumption of modern pharmaceuticals. If we deduct these figures from the total production of developing countries, we end up with 22.29% production and 23.25% consumption for the other developing countries.

Therefore, according to 1990 figures, 25% of the world population in developed industrialized countries consume 72% of the modern pharmaceuticals and 75% of the world population living in developing countries have to consume only 28% of the global pharmaceutical production.

Ca. 2000 new drugs (New Molecular Entities = NMEs) were introduced into the pharmaceuticals market between 1960 and 1988 and over 90% of them were discovered in one of the ten developed countries: USA, Japan, Germany, France, Italy, UK, Switzerland, Sweden, the Netherlands and Belgium.

In 1989, research spending in pharmaceutical industry was almost $5 billion in USA and it reached almost $1.5 billion each in Germany and Japan. In recent years, research spending has rocketed, Merck invested approximately $ 1.5 billion in research into new drug development in 1996 (Scimone 1997).

Two decades ago, none of the top 250 pharmaceutical companies had research programmes involving higher plants. Now, over half of them have such programmes. This revival of interest is stimulated by the effective use of standardized plant extracts in chronic conditions (Editorial 1994).

It is interesting to note that over half the world's best selling pharmaceuticals owe their origin to one of a range of natural source materials (O'Neill *et al.* 1993). Two of which, cyclosporin and mevinolin are natural products whereas 12 are natural product derived.

2.5. Screening for New Pharmaceutical Leads

Over the last fifteen years, high-throughput screening involving enzyme techniques has been successfully used in the search for new chemical entities (NMEs). High-throughput screening assays allow a response against a biological target which can be measured and quantified or simply a negative response is obtained. Target may be a certain cell type, an enzyme playing a key role in a specific biosynthetic process, a receptor-ligand interaction or a molecule involved in gene transcription (O'Neill *et al.* 1993). Such screens allow the researcher to find new chemical leads which can then be developed in the laboratory to new medicines.

Combinatorial chemistry techniques have been used by pharmaceutical companies for new drug development since 1994. It combines wet laboratory synthesis and computer softwares to offer a wide array of molecules for testing. In the last three years several large pharmaceutical companies have established collaborations with smaller combinatorial firms (Scimone 1997).

Certain firms are using combinatorial chemistry in natural products research. Since June this year, Parke-Davis has been using UK based Xenova's libraries of natural compounds to develop and commercialize compounds from plants, fungal and marine products. Phytera has developed a new antifungal product, sunillin, combining plant cell culture technology with bioactivity optimization through combinatorial chemistry and high throughput screening (Scimone 1997).

In the USA, the National Cancer Institute had screened over 35.000 plants and over 200.000 microorganisms for potential anticancer drugs since the late '50s. This extensive work has resulted in the development of only three drugs.

From the roots of *Podophyllum peltatum*, etoposide and teniposide were developed. These are semi-sythetic derivatives of epipodophyllotoxin, an epimer of podophyllotoxin. Etoposide is active against small-cell lung and testicular cancers, and teniposide shows activity against acute lymphocytic leukemia and neuroblastoma in children, and non-Hodgkin lymphomas and brain tumors in adults (Cragg *et al.* 1991).

The second plant with promise in cancer therapy was the Chinese tree Camptotheca acuminata which yields the alkaloid camptothecin. This compound and its derivatives have recently received FDA approval for research as anticancer agents in ovarian, colon and small cell lung indications (Cragg *et al.* 1991).

Taxol (Paclitaxel) is first isolated from inner bark of *Taxus brevifolia*. It is now produced from wood chippings and leaves of other *Taxus* species. In USA, large scale cultivation of Taxus species is carried out for the production of paclitaxel (Piersch *et al.* 1994). In India, A taxane rich extract from leaves of the Himalayan *Taxus wallichiana* harvested in Nepal is converted to paclitaxel via the action of a fungus *Taxomyces andreanea*. The price of taxol ranges from $600.000 to $800.000 per kilo (Anon. 1997). In 1996 worldwide sales of anticancer Taxol® (Paclitaxel) were US$ 813 million. The annual market for taxol products is estimated to reach US$ 1 billion by the year 2000 (Scimone 1997, Cragg *et al.* 1991, Robbers *et al.* 1996). In 1992, FDA approved its use in the treatment of ovarian cancer, and in 1994 for metastatic breast cancer. Taxol has come off patent this year. However, a taxol infusion set patent was extended on June 24, 1997 for another 20 years (Scimone 1997).

Boehringer Ingelheim has been marketing scopolamine derivative - Hyoscine N-butylbromide, an anticholinergic and antispasmodic, and yohimbine, an aphrodisiac with great success. It is also developing lobeline as a non-nicotine smoking secession drug and arecoline as an intermediate for antidepressant and anti-alzheimer drugs (Scimone 1997).

Shaman Pharmaceuticals established in 1989 had developed two plant based products following the screening of 450 plants. Virend, for treatment of genital herpes in phase III clinical trials, and Provir extracted from *Croton* sp. for travellers diarrhoea in phase II. The former with an estimated world market of US$ 1.3 billion, and the latter with a US$ 26 million market (Griggs 1997).

Plant drugs are used variously (Fig.1). They can be used as such or in galenical preparations such as infusions, decoctions, extracts, oily macerates, essential oils, etc. They provide useful phytochemicals, which are difficult to synthesize economically, such as morphine, digitoxin, digoxin, ergot alkaloids, vinca alkaloids, most antibiotics. As mentioned above they may provide leads which may be modified slightly to render them more effective or less toxic, such as taxol from baccatin III, or can be used as precursors of useful active chemicals, such as diosgenin as the starting point for semi-synthesis of hormones and birth-control pills. They may be the source of phytochemicals as prototypes or models for totally synthetic drugs possessing physiological activities similar to the original compound. A list of such chemicals are given in Table 1 (Robbers *et al.* 1996).

Natural products are becoming increasingly important in drug development. 1995 worldwide sales of important categories of established plant-derived products amount to millions of dollars, some examples are as follows: Steroids at $22, opiates at $1.5 billion, combined sales of nicotine and scopolamine patches at over $1 billion, psyllium seed products at $300 million, taxanes at $400 million, digoxin and related compounds at $200 million, ergot alkaloids at $150 million and Catharanthus derived products at $100 million (Scimone 1997, Robbers *et al.* 1996).

In 1996, worldwide sales of Pravachol® (Pravastatin sodium), naturally derived cholesterol-reducing drug were $1.1 billion (Scimone 1997).

Worldwide, at least 121 phytochemicals of known structure are currently obtained from medicinal plants. It is almost impossible to make an estimation of the number and the volume of extracts used in traditional medicine.

Phytopharmaceutical companies in Europe favour the use of standardized extracts of medicinal plants instead of single phytochemicals. Some successful examples in the last decade are as follows (Griggs 1997, Grünwald *et al.* 1996, Robbers 1996, Tyler 1993):

Ginkgo. A standardized extract of the leaves of Ginkgo biloba containing 24% flavonoids and 6% terpenoids called ginkgolides has successfully been marketed since 1965 by Schwabe (Germany) under the name Tebonin® in Germany and Tanakan® in France. It is used in the treatment of decreased cerebral blood flow causing memory loss, headache, dizziness and depression particularly in geriatric patients. Worldwide sales of this medicine in 1993 were $ 195 million. Although, in 1988, 5.4 million prescriptions were written for it in Germany alone, it is also available as an OTC drug. Its sales are expected to rise as life expectancy in developed countries increases. The tree is cultivated in France and USA for pharmaceutical processing.

Garlic. Used as food for centuries, garlic (the bulbs of *Allium sativum*) has become an important commodity of the phytopharmaceutical industry in recent years. It is one of the most researched medicinal plants. Garlic products are used to lower blood pressure and cholesterol. In 1993, the annual sales of Lichtwer Pharma's Kwai® were $40 million worldwide. In Germany alone, some 7 million people take garlic regularly. Garlic products constitute 84% of the natural anti-arteriosclerotics in German Pharmaceuticals Market. Lichtwer Pharma imports around 1500 tons of high-yielding garlic grown organically in China.

St.John's Wort. Flowering tops of this plant (*Hypericum perforatum*) have long been used externally for wound healing in an oil base. In recent years, antidepressant properties of this plant have been discovered and the pharmaceutical industry was not late to respond to this new promising natural antidepressant. In late '80s, Hypericum-based antidepressants have started to appear in the market, especially after Commission E approved the use of St.John's wort for the treatment of psychotic disturbances, depression, anxiety, and nervous unrest. Although, at present there are over 60 products in the market, pharmaceuticals like Jarsin®, Kira® and Hyperforat® have the greatest market share, with over 50% of total sales. Annual sales of Jarsin¨ were running at DM125 million by 1996, by which time it was outselling Prozac® both in volume and value. At first, the activity was attributed to hypericin, a naphthodianthron pigment, however it has been proven that hypericin-free Hypericum extracts can also exhibit antidepressant activity (Tyler 1993 and 1994, Ozturk *et al.* 1996). We have recently reported hepatoprotective activity of an alcoholic extract of *Hypericum perforatum* (Ozturk *et al.* 1996). Hypericin has been under clinical trials since early '90s for use in the treatment of retroviral-induced diseases like AIDS.

Echinacea. This American plant with a long history of traditional use among the American indians has gained considerable reputation in Europe in recent years. Freshly expressed juice of the herbal parts of *Echinacea purpurea* has been formulated into products as an immunostimulant. It has been shown to stimulate the immune system and found useful in the treatment of influenza. Although there are several Echinacea products in the market, total sales of Echinacin® of Madaus were $30 million in 1993. The use of this drug in various forms has also been approved by the German Commission E. There are over 150 phytopharmaceuticals containing Echinacea currently in Germany. Echinacea products are produced from cultivated plants however commercial scale tissue culture of *Echinacea purpurea* has also been successful.

Ginseng. This centuries old Chinese remedy has in the last two decades become one of the best selling plant drugs in the world. Roots of *Panax ginseng* (Chinese or Korean ginseng) and *Panax quinquefolium* (American ginseng) are the most widely used ginseng drugs used as tonic. Hundreds of ginseng products are sold as OTC in world markets. Among the phytopharmaceuticals, the total sales of Ginsana® were 50 million dollars in 1993. The same year, $90 million worth of American ginseng was exported from USA (Robbers *et al.* 1996).

3. Aromatic plants

Aromatic plants are used as herbal tea, spice and condiment or as sources of essential oils and extracts. When their biological activity is proven by experimental evidence, they may be used in therapy and regarded as a medicinal plant as well. However, greater use of aromatic plants is in the flavour and fragrance sector.

Essential oils are obtained by various forms of distillation such as water distillation, water-and-steam distillation, steam distillation, dry distillation, cold pressing or by concentration of fruit juices. These techniques can be applied in different forms such as turbo distillation, hydrodiffusion or vacuum microwave distillation. Flavouring products can also be obtained by extraction with organic solvents or liquified gasses at low or high pressures such as in phytol-extraction or supercritical fluid extraction, respectively.

Phytol extraction process uses HFC 134a (1,1,1,2-tetrafluoroethane), a refrigerant gas with a boiling point of -26.2°C. It is a clear, colourless, inert, non-flammable liquid. It has low toxicity, no odour and its vapour pressure at room temperature is 5 bar - comparable to champagne's room temperature vapour pressure of 6 bar. Plant material is put in contact with this liquified gas in a closed system. Eventually, the extract is pulled into another container, the solvent is removed and collected for re-use. If aromatic plants are used this process yields an extract which is akin to essential oils. Phytol extraction process has a UK and European food approval and is under examination for FDA approval (Ozturk *et al.* 1992).

Supercritical fluid extraction (SFE) process is performed at high pressure. The pressure involved is 350-500 bar. CO_2 extraction plants initially require high investment. Supercritical carbon dioxide extracts are approved for food use. It has to be remembered that due to high pH (pH 2) of Supercritical CO_2, some unwanted side reactions, such as hydrolysis of esters, may occur. However, by changing pressure and temperature, it is possible to attain the solvating power of any organic solvent. By the use of polar modifier solvents, such as water, ethanol, methanol, acetone, etc. it is possible to perform a complete extraction of all extractables. Due to high investment and sophistication of the process, SFE products are expensive. The most well known industrial application of SFE process is the production of decaffeinated coffee.

Essential oils and aromatic extracts are used in flavour and fragrance industries as ingredients of perfumes, food additives, household products and medicines, as sources of aroma chemicals or precursors for useful semi-synthetic or nature-identical chemicals.

3.1. World Production of Essential Oils

The world production of essential oils is estimated at around 45 to 50 thousand tons, which is valued at over $ 1 billion. These figures exclude products derived from turpentine for which the estimated world production is over 300.000 tons (Houlton 1997).

Fifteen essential oils each with an annual production of more than 500 tons account for 90% of the total world production (Table 2). The eighteen most important species represent nearly 75% of the total value.

65% of the total essential oil production is derived from woody plants, that is trees and bushes. They include high volume-low value products such as citrus oils and low volume-high value products such as rose, jasmine and vetiver oils. Citrus and mint oils dominate the world essential oil market.

Developing countries have the greatest potential for the production of essential oils. 55% of the total world production is produced in developing countries, 35% in industrialized countries and 10% in Eastern European countries. Seven leading countries, namely China, Brazil, India, Indonesia, Turkey, Egypt and Morocco, are responsible for 85% of the world production in developing countries.

Major exporters of essential oils are: China, European Union, USA, Brazil, Indonesia and India. They account for 66% of the essential oil exports.

Industrialized countries are the main importers of essential oils. European Union, USA, Japan, Switzerland and Canada account for more than 70% of the total volume imported. European Union alone imports 43% of the total import volume of essential oils. Annual world import of essential oils is estimated at 95.000 tons with an import value of over US$ 900 million dollars.

It is estimated that 3% of the world essential oil production is used by the pharmaceutical industry. 34% are used in soft drinks and the rest is used in flavour and fragrance industries.

3.2. Worldwide Sales of Flavours and Fragrances

The total worldwide sales of flavour and fragrance industries were realized at US$ 11.4 billion in 1995. This corresponds to US$ 2.1 billion increase compared to 1993 figures. Flavours constitute 35% of the market, while fragrances make up of 32% and aroma chemicals make up of 18% (Verlet 1995). Essential oils and natural extracts have a share of 15%. Over 50% of the market is dominated by six multinational companies: IFF, Givaudan-Roure, Quest, Haarman and Reimer, Firmenich and Takasago. Other important companies include Bush Boake Allen, Dragoco, Tastemaker, Robertet, Mane and Charabot (Nakajima *et al.* 1994, Calame 1994).

Due to consumer demand for natural flavours, flavour industries are turning to naturalize their existing synthetic ingredients. Multinational food products manufacturer, Nestle, now uses 75% of natural flavours, 12.5% of enhanced natural, 7.2% of 'nature identical' flavours and only 5.3% of artificial flavours (Runham 1996).

The recent upsurge of aromatherapy trade in industrialized countries is expected to increase the demand for a variety of essential oils. Developed countries employ improved selection and breeding techniques, and advanced agrotechnology for crops like mint, citrus and lavender to ensure the production of cost-effective high quality products with improved yields. Demand for organically grown plants and their products is also increasing.

3.3. Non-Conventional Uses of Essential Oils

Non-conventional uses of essential oils are also finding application in agriculture. Several essential oils are used as insecticides, fungicides, herbicides and nematocides, and to stop sprouting of potatos during storage and as antioxidants (Runham 1996, Palevitch 1994).

Botanical pesticides are safer for human use and cause less resistance in insects. 80% of all botanical pesticides are derived from pyrethrum. Tansy (*Tanacetum vulgare*), wormwood (*Artemisia absinthium*) and basil (*Ocimum basilicum*) are known to repel

insects, fleas and moths. Garlic, cinnamon, oregano, thyme, black pepper and cumin are used to preserve food against fungal infection, hence curb aflatoxin contamination.

Garlic, carvone, pulegone has been shown to suppress sprouting of potatoes during storage. Some 3-4 million tons of potatoes are stored in the UK annually. They require repeated treatments with antisprouting chemicals such as clorpropham or tecnazene. It is estimated that some 130 tons of these chemicals were used in 1990. Carvone isolated from the essential oils of caraway or dill is expected to replace these chemicals in near future. Pulegone has also been shown to inhibit the growth of wheat seeds in Israel (Runham 1996).

The use of some essential oils or aromatic plant extracts as antioxidant is gaining ground among the food manufacturing industries. Rosemary extracts have been used by some food manufacturers as an antioxidant. Antioxidants preserve food from spoilage through oxidation. They also have free radical scavenger activity in the body. Free radicals are believed to cause cancer and aging.

4. Concluding remarks

As illustrated in this lecture, the industrial utilization of medicinal and aromatic plants and their products has increased in the last decade, especially in developed countries where synthetic products used to dominate the markets previously. The prospects for their greater use are high. This will require greater production of medicinal and aromatic plant materials. Developing countries possess vast arable land, favourable climatic conditions, and are basically agriculture based economies. Good quality planting materials, appropriate agrotechnologies, suitable post-harvest treatment, storage and transport are basic requirements for the production of good quality materials which conform to acceptable standards.

Major constraints in developing countries barring the development of medicinal and aromatic plant processing industries are the lack of scientific and technological knowledge, trained personnel, quality control and marketing facilities.

Collection of plant materials from the wild seems to be an economical way to obtaining raw materials. However, the nature is full of diversity and wild plants are its living proofs. Due to changes in the composition and amount of active constituents from plant to plant, the collection may only represent an average. So much material is wasted during collection from wild plants and during transport to processing or post-harvest treatment sites. Furthermore, wild-collected plant materials may frequently contain foreign plant parts, which may sometimes prove quite difficult to clean up.

Therefore, the agriculture of plants for which there is great demand is essential in order to maintain constant quality and consistency. Appropriate processing technologies may be installed at the farm site for processing medicinal and aromatic plants. Especially in the case of aromatic plants, distillation plants may be installed to produce essential oils, or extracts can be obtained using suitable technologies in tropical countries where drying and storing of plant materials may be troublesome.

As conclusion, it can be safely stated that markets for medicinal and aromatic plant products are expected to expand requiring processing industries to develop in order to meet the ever growing demand.

5. References

Anon., 1997, Whole Foods Magazine's 2nd Annual Herb Market Survey for U.S. Health Food Stores. HerbalGram 40: 52.

Anon., 1997, Taxol-Type Products Sparkle, Lure New Players to Scene. CMR 251(16): 4, 10.

Baker J.T., R.P. Borris, B. Carte, G.A. Cordell, D.D. Soejarto, G.M. Cragg, M.P. Gupta, M.M. Iwu, D.R. Madulid and V.E. Tyler, 1995, Natural Product Drug Discovery and Development: New Perspectives on International Collaboration. J.Nat.Prod. 58(9): 1325-1357.

Ballance R., J. Pogany and H. Forstner, 1992, The World's Pharmaceutical Industries. UNIDO-Edward Elgar, UK.

Blumenthal M., 1997, Herbal Monographs. HerbalGram 40, 30-38.

Calame J.P., 1994, Trends in Perfumery. In: Proceedings of the 4th Symposium on the Economy of Medicinal and Aromatic Plants, 5-7 December 1994, Nyons,: 87-91.

Cragg G.M., M.R. Boyd, J.H. Cardellina II, M.R. Grever, S.A. Schepartz, K.M. Snader and M. Suffness, 1993, The Role of Plants in the National Cancer Institute Drug Discovery and Development Programme. In: Human Medicinal Agents from Plants, A.D. Kinghorn and M.F.Balandrin, Eds., ACP Symposium Series 534, Washington: 80-95.

Editorial, 1994, Pharmaceuticals from Plants: Great Potential, Few Funds. Lancet 343: 1513-1515.

Griggs B., 1997, New Green Medicine. Vermillion, London.

Grünwald J. and K. Büttel, 1996, European Phytotherapeutics Market. Drugs Made in Germany 39(1): 6-11.

Houlton S., 1997, Capturing the Essence of Plants in an Oil. Manufacturing Chemist, (9) 29-30.

Johnson B.A, 1997, One-Third of Nation's Adults Use Herbal Remedies. HerbalGram 40, 49.

Keller K. 1996, Phytotherapy at an European Level. Zeitschrift für Phytotherapie 17, 356-366.

Laird S.A., 1995, Research Agreements on Conservation Projects and Biodiversity Prospecting: Roles for WWF. WWF for Nature, Switzerland

Lambert J., J. Srivastava and N. Vietmeyer, 1997, Medicinal Plants. Rescuing a Global Heritage. World Bank Technical Paper 355, Washington.

Lehner M., 1997, Labeling Rules for Supplements May Jump Start Fledgling Sector. Chemical Marketing Reporter 252(16): 16.

Miceli D.L., 1997, A Favourable Outlook for OTCs. CMR Focus Report 252(11): 34-35.

Nakajima M., N. Toi and Y. Sugiaura, The Japanese Market for Perfumery Products. In: Proceedings of the 4th Symposium on the Economy of Medicinal and Aromatic Plants, 5-7 December 1994, Nyons: 71-75.

O'Neill M.J. and J.A. Lewis, 1993, The Renaissance of Plant Research in the Pharmaceutical Industry. In: Human Medicinal Agents from Plants, A.D.Kinghorn and M.F. Balandrin, Eds., ACP Symposium Series 534, Washington:. 48-55.

Ozturk Y., S. Aydin, R. Beis and K.H.C.Baser, 1996, Effect of *Hypericum calycinum* L. Extract on the Central Nervous System in Mice. Phytother. Res. 10:700-702.

Ozturk Y., S. Aydin, R. Beis, K.H.C. Baser and H. Berberoglu, 1996, Effects of *Hypericum perforatum* L. and *Hypericum calycinum* L. Extracts on the Central Nervous System in Mice. Phytomedicine 3(2):139-146.

Ozturk Y., S. Aydin, K.H.C. Baser, N. Kirimer and N. Kurtar-Ozturk, 1992, Hepatoprotective Activity of *Hypericum perforatum* L. in Rodents. Phytother. Res. 6, 44-46.

Palevitch D., 1994, Non-conventional Uses of Volatile Oils and their Constituents in Agriculture. In: Proceedings of the 4th Symposium on the Economy of Medicinal and Aromatic Plants, 5-7 December 1994, Nyons: 26-40.

Piersch R.F., N.C. Wheeler and V.P. Wyant-Wheeler, 1994, Large Scale Cultivation of Taxus Species for Taxol® Production. In: Proceedings of the 4th Symposium on the Economy of Medicinal and Aromatic Plants, 5-7 December 1994, Nyons: 20-25.

Robbers J.E., M.K. Speedie and V.E. Tyler, 1996, Pharmacognosy and Pharmacobiotechnology. Williams and Wilkins, Baltimore.

Runham S.R, 1996, An Updated Review of the Potential Uses and Markets of Plants Grown for Extracts Including Essential Oils and Factors Affecting Their Yield and Composition. Ministry of Agriculture, Fisheries and Forestry (MAFF), UK.

Scimone A., 1997, Six Degrees of Separation in Drug Discovery. CMR Focus Report 252 (11): 10-13.

Srivastava J., J. Lambert and N. Vietmeyer, 1996, Medicinal Plants. An Expanding Role in Development, World Bank Technical Paper 320, Washington.

Steinhoff B., 1996, European and Worldwide Aspects on the Present Regulation of Herbal Products. AESGP Annual Meeting, 29 May-1 June, Istanbul, Turkey.

Tyler V.E., 1993, Phytomedicines in Western Europe. In: Human Medicinal Agents from Plants, A.D. Kinghorn and M.F. Balandrin, Eds., ACP Symposium Series 534, Washington: 25-37.

Tyler V.E., 1994, Herbs of Choice. Pharmaceutical Products Press, New York.

Verlet N., 1995, Commercialization of Essential Oils and Aroma Chemicals. In: Manual on the Essential Oil Industry, K.Tuley De Silva, Ed., UNIDO: 203-232.

Xiao P-G., and Y. Peng, 1994, How is Ethnobiology Contributing to Traditional Chinese Medicine? In: Final Report, TCDC Workshop on Medicinal Plants, 11-14 October 1993, Eskisehir, Turkey, UNDP/TCDC-New York: 14-19.

Zhang X., 1996, Regulation and Registration of Herbal Medicines. AESGP Annual Meeting, 29 May-1 June, Istanbul, Turkey.

Table 1 - Examples of Plant Drugs Serving as Prototypes or Models for Other Medicinals

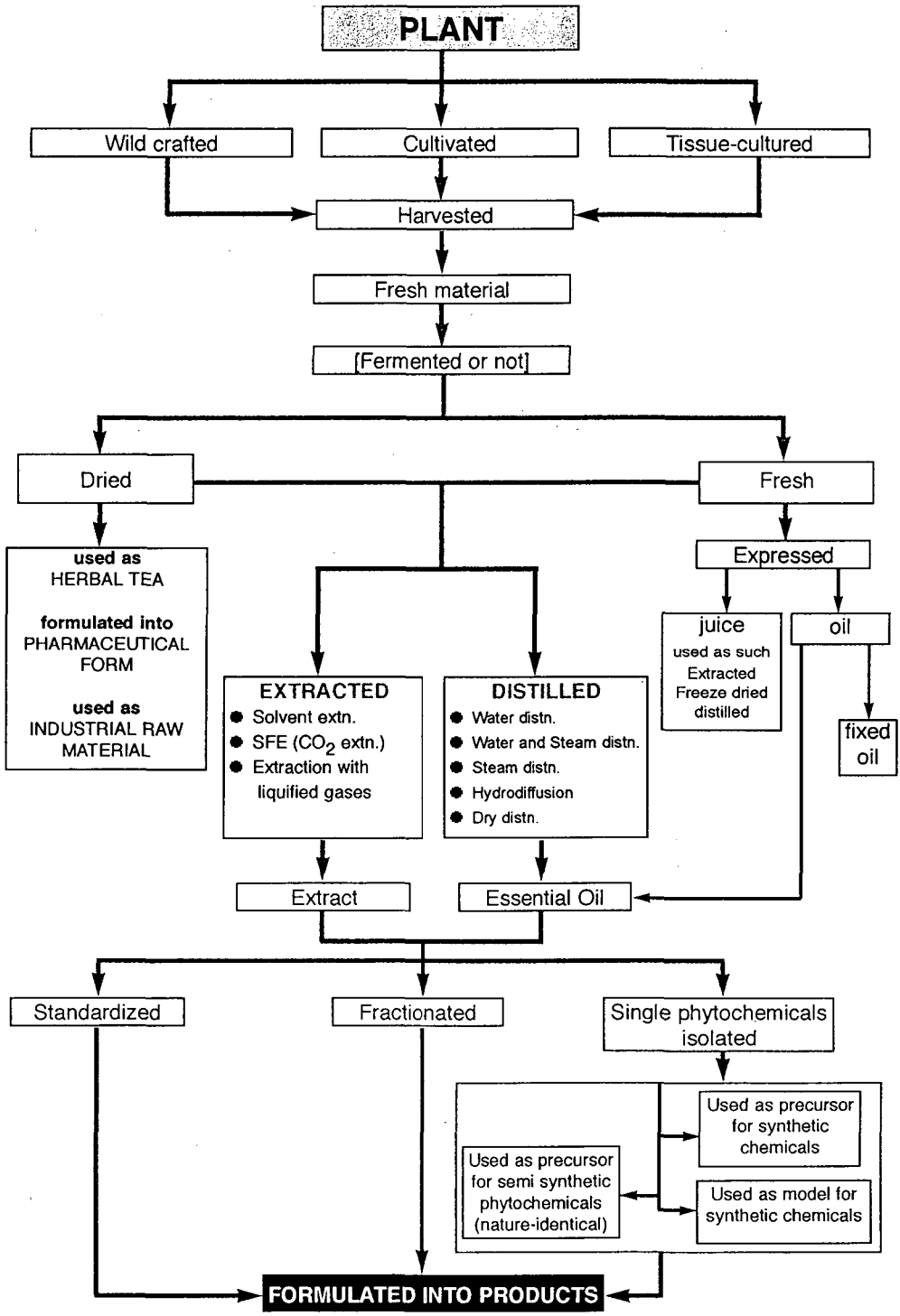
Natural	*Semi-Synthetic*	*Prototype-derived Synthetic*
Atropine	Homatropine	Glycopyrrolate
Cocaine	-	Procaine
Ephedrine	Phenylpropanolamine	Tetrazoline
Epipodophyllotoxin	Etoposide and Teniposide	-
Ergotamine	Dihydroergotamine	-
Guaiacol	Guaifenesin	-
Khellin	-	Cromolyn
Morphine	Hydromorphone	Propoxyphene
Physostigmine	-	Neostigmine
Quinine	-	Chloroquine

Reference: J.E. Robbers, M.K. Speedie and V.E. Tyler, Pharmacognosy and Pharmacobiotechnology. Williams and Wilkins, Baltimore (1996).

Table 2

Oil	Species	Estd. Annual Prodn. (Ton)
Orange	*Citrus sinensis*	15000
Mint (peppermint,	*Mentha piperita*	
spearmint, cornmint)	*M.spicata, M.arvensis*	6000-8000
Eucalyptus	*Eucalyptus globulus*	3000
Lemon	*Citrus limon*	2000-2500
Eucalyptus (Lemon scented)	*Eucalyptus citriodora*	2000
Clove	*Syzygium aromaticum*	2000
Citronella	*Cymbopogon winterianus*	1600-1750
Cedarwood (American)	*Juniperus virginiana*	
	J.mexicana, J.procera	700-1400
Lemongrass	*Cymbopogon flexuosus*	
	C.citratus	800-1300
Sassafras	*Ocotea pretiosa*	1200
Lime	*Citrus aurantiifolia*	900
Lavandin	*Lavandula* sp.hybrid	750
Coriander	*Coriandrum sativum*	750
Litsea cubeba	*Litsea cubeba*	500-600
Patchouli	*Pogostemon cablin*	500-550

Figure 1


PLANT
Wild crafted
Cultivated
Tissue-cultured
Harvested
Fresh material
[Fermented or not]
Dried
Fresh
used as
HERBAL TEA
formulated into
PHARMACEUTICAL
FORM
used as
INDUSTRIAL RAW
MATERIAL
Expressed
juice
used as such
Extracted
Freeze dried
distilled
oil
fixed
oil
EXTRACTED
Solvent extn.
SFE (CO_2 extn.)
Extraction with
liquified gases
DISTILLED
Water distn.
Water and Steam distn.
Steam distn.
Hydrodiffusion
Dry distn.
Extract
Essential Oil
Standardized
Fractionated
Single phytochemicals
isolated
Used as precursor
for synthetic
chemicals
Used as precursor
for semi synthetic
phytochemicals
(nature-identical)
Used as model for
synthetic chemicals
FORMULATED INTO PRODUCTS