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A Detailed Study on Natural Products and Medicinal Plants in the Light of Secondary Metabolites

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Abstract: ***A comprehensive review of the literature reveals that it is well known that, there is a tremendous need to discover and invent new agents is genuine and necessary for all kinds of living beings in order to survive from the natural environmental and in borne diseases. India, about 20% of the drugs available are from plant derived and are particularly useful to treat chronic diseases of liver, kidney and skin. People prefer Ayurvedic or herbal medicines, as they have practically no adverse effects. We found that, medicinal plants represent precious resources from which bioactive compounds can be isolated and developed into valuable therapeutic agents, with the advent of modern drug discovery technologies such as combinatorial chemistry and Drug screening platforms.***

Keywords: Primary metabolites, Secondary metabolites, Herbal plants

1. Introduction

It is well known that, India is extremely rich in medicinal plant diversity distributed in various geographical and environmental conditions and associated with much tribal and folklore knowledge, the people who are living in the remote villages and forests, totally dependent upon the medicinal plants for the survival of their ethnic communities. Even today, large number of Indian population relies on traditional herbal medicine and has attracted considerable global interest in recent years[1.] For thousands of years, countries around the world have used herbs and plants to treat illness and maintained their health. It has been observed that a wide spectrum of bioassay can be employed for the detection of bioactivity in extracts, fractions, as well as purified compounds of herbal origin. According to World Health Organization (WHO), most of these drugs were developed because of their use in traditional medicine. Recent WHO studies indicates that over 30 percent of the world plant species have at one time or another been used for medicinal-purposes. Of the 2, 50, 000 higher plant species on Earth, more than 80, 000 species have medicinal importance. Although traditional medicine is widespread throughout the world; it is an integral part of each individual culture. For hundreds or even thousands, its practice is used mainly on traditional belief handed down from generation to generation. Oldest of such literature is the Ayurvedic text Charakasamhita. India's use of plants for health care also dates back close to 5000 years. About 8000 herbal remedies have been confirmed in Ayurveda, which is still in use in many dispensaries today.

In the early 19th century, the structure determination and synthesis of Natural products have gained natural attention, the screening of medicinal or poisonous plants of Tropical forests, Marine flora and fauna, soil samples, fungi and microbes produce new drugs or lead structures and these gave more potent synthetic and semi-synthetic products[2], ternesiriih, taxol and camptothecin are examples of natural products that are used clinically. Several natural products isolated from plants used in traditional medicine have potent anti-plasmodial action in vitro and represent potential sources of new antimalarial drugs and these were studied by Phillipson and co-workers[3]. There are 121 drugs of known structures-extracted from higher plants that are still used globally in allopathic medicine. In addition to above a good number of novel plant derivative substances have entered into western drug markets and clinical plant based researches as made a rewarding progress in all important fields, particularly in anti-cancer and antimalarial therapies as reported by De Samet and Co-workers[4].

Naturally occurring medicinal sources, based on their source, are divided into 4 types as follows:

Microbial world [Cephalosporins]
Plant sources [paclitaxel]
Marine sources [Discodermalide]
Animal source [Epibatidine]

These 121 plant derived drugs are produced commercially from less than 90 species of higher plants. It is estimated that 80% of anti-tumor and anti-infectious drugs already in the market or under clinical trial are of natural origin obtained directly or indirectly[5, 6].

The first isolated compound is an alkaloid which includes Morphine, Strychnine, quinine etc. The early 19th century marked a new era in the use of Medicinal plants and the beginning of modern medicinal plant research. Equally, the efficacy of a number of Phytopharmaceutical preparations, such as aloe, ginko, garlic or valerian, has been demonstrated by studies that applied the same scientific standards as for synthetic drugs. As a result of all, there is an enormous busy market for crude herbal medicines in addition to purified plant derived drugs[7].

Prior to World War II, a series of natural products isolated from higher plants became clinical agents and a number are still in use today. Quinine from Cinchona bark,

morphine (*Papaverasomniferum*) and codeine from the latex of the opium poppy, digoxin from Digitalis leaves; atropine (*Atropa belladonna)* and hyoscine from species of the Solanaceae continue to be in clinical use. Recently, natural products are attracting the many of Pharma industry. Large pharmaceutical such as Merck, CIBA, Glaxo, Bochringer and Syntex, now have specific departments dedicated to the study of new drugs from natural sources. Glaxo Company is well known for the production of drugs in bulk which are identified as drugs from natural products, e.g.: Penicillin, vitamin B_{12} etc. and it is giving much importance to further natural products research. Taxol is obtained from the bark of the Western Pacific Yew, Taxusbrevifolia. The isolation and structure determination of taxol followed on from experiments that showed that a crude extract was active against cancer cells in laboratory tests. The resin podophyllin obtained from the root of the mayapple, Podophyllumpeltatum, is toxic and is used clinically to remove warts. The major constituent of the resin is the lignin podophyllotoxin which inhibits cell division.

The clinical applications of taxol, etoposide and artemesinin have helped to revive an interest in higher plants as sources of new drugs. Though there is a considerable development in medicinal field, there still remains an urgent need to develop new clinical drugs for numerous diseases which result from the malfunction of the Central Nervous Systems (CNS), e.g. Alzheimer and Parkinson's disease, epilepsy, migraine, pain, schizophrenia, sleeping disorders, etc. Natural products already have a proven track record for CNS activities, e.g., caffeine, codeine, morphine, nicotine, reserpine and it is possible to further such drugs still to be found from nature[8].

According to World health Organization (WHO) herbal medicines serve the health needs of about 80% of the world's population[9]especially for millions of people in the vast rural areas of developing countries. Meanwhile, consumers in developed countries are becoming disillusioned with modern health care and are seeking alternatives. The recent resurgence of plant remedies results from several factors;

1) The effectiveness of plant Medicines
2) The side effect of most modem drugs
3) The development of Science and Technology

The latest advances in bio-technology have contributed greatly in the production of commercially important compounds, in plants or plant cell culture, or even to produce completely new compounds. Culturing of Plant cells can produce many valuable metabolites including novel medicinal agents and recombinant products. In combination with synthetic chemistry, methodology also affords an attractive route to the synthesis of complex natural products and related compounds of industrial importance as reported by Kumar and Co-workers.[10]

Many scientific methods of analysis have been developed for the investigation of the constituents and biological activities of medicinal plants. The Chromatographic (e.g., TLC, GLC, HPLC), Spectroscopic (e.g., UV, IR, ^{1}H, ^{13}C-NMR, 2DNMR, 3D NMR and MS,) and biological (e.g., anticancer, anti-inflammatory, immune stimulant, antiprotozoal) techniques utilized for medicinal plant research are reviewed from time to time. The contribution that advances in scientific methodology have made to our understanding of the actions of some herbal medicines (e.g., Echinacea, Ginkgi, St.John's Wort, Cannabis), as well as to Ethno pharmacology and bio technology are revived in scientific journals. Plants have provided many medicinal drugs in the past and remains as a potential source of novel therapeutic agents. Despite all of the powerful analytical techniques available, the majorities of plant species has not been investigated chemically or biologically in any great details and even well-known medicinal plants require medicinal further clinical study as opined by Phillipson and Co-workers.[11]

According to Kang and Co-workers[12]certain medicinal plants contain anti-inflammatory and antioxidative substances that can exert chemo preventive effects. The methanol extract of Alpiniaoxyphylla Miguel (Zingiberaceae) inhibits tumor promotion in mouse skin. Two major di-aryl-heptanoids named yakuchinone A (1 – [4'-hydroxy-3'- methoxypheny1]-7-pheny1-3-heptanone) and yakuchinone B (1-[4'-hydroxy-3'- methoxypheny1]-7-phenylhept- 1-en-3 -one) have been isolated from this medicinal plant. Both compounds have strong inhibitory effects on the synthesis of prostaglandins and leukotrienes in vitro. The sesquiterpene lactone parthenolide, the principal active component in *Partheniumhisterephorus*, has been used conventionally to treat migraines, inflammation, and tumors, parthenolide and its derivatives may be useful chemotherapeutic agents to treat these invasive cancers. This was reported by Wen and co-workers[13].

Youdim and co-workers [14]reported that Antioxidants minimize the oxidation of lipid components in cell membranes by scavenging free radicals. However, imbalance- between free radical production and removal tends to increase with age causing progressive damage. For the food industry, it is of considerable interest to delay the autooxidation of food lipids, which is the cause of reduction in food quality, affecting color, taste, nutritive value, and functionality. The major components identified in thyme oil were found to inhibit ferric-ion-stimulated lipid peroxidation of rat brain homogenates, although none was as effective as the whole oil. The order of antioxidant activity was; thyme oil >thymol>carvacrol> γ-terpinene>myrcene> linalool > p-cymene > limonene > 1, 8-cineole >α-pinene.

The genus Tan acetum has been used as medicinal plants for over 2000 years. Interest in the genus has been stimulated by its biological activities, particularly as insect antifeedants, antitumor and antimicrobial agents due to its sesquiterpenoid constituents which are the main constituents of the genus are supposed to be bioactive principles of the plants. Flavonoids and essential oils are also pointed out as active substances in some species. The chemical and biological activities were studied by Goren and co-workers.[15]

Results of various projects of Mexican Indian ethnobotany and some of the subsequent pharmacological and phytochemical studies are summarized focusing both on chemical, Pharmacological, as well as anthropological (ethnopharmacolgy) aspects. These were reported by Henrich and co-workers[16]. There exists well defined criteria specific for each culture, which lead to the selection of a plant as a medicine. This field research has also formed a basis for studies on bioactive natural products from selected species. The bark of *Guazumaulmifolia* showed antisecretory activity (cholera toxin-induced chloride secretion in rabbit distal colon in an USSING chamber). Active constituents are procyanidins with a polymerisation degree of eight or higher. *Byrsonimacrassifolia* yielded proanthocyanidins with (+) epicatechin units and *Baccharisconferta* showed a dose-dependent antispasmodic effect with the effect being particularly strong in flavonoid-rich fractions. Their ethno-pharmacological research led to the identification of sesquiterpene lactones (SLs) like parthenolide as potent and relatively specific inhibitors of the transcription factor NF-kB, an important mediator of the inflammatory process.

Petersen and co-workers[17] proposed Rosmarinic acid is an ester of caffeic acid and 3, 4-dihydroxyphenyllactic acid. Rosmarinic acid has a number of interesting biological activities, e.g., antiviral, antibacterial, anti-inflammatory and antioxidant. The presence of rosmarinic acid in medicinal plant herbs and species has beneficial and health promoting effects. In plants, rosmarinic acid is supposed to act as a preformed constitutively accumulated defense compound. The biosynthesis of rosmarinic acid starts with the amino acids L-phenylalanine and L-tyrosine. All eight enzymes involved in the biosynthesis are known and characterized and cDNAs of several of the involved genes has been isolated.

Amentoflavone is found in number of plants with medicinal properties, including *Ginkgo biloba* and *Hypericumperforatum* (St. John's Wort). Hanrahan and co-workers[18] developed a rapid and economic semi-synthetic preparation of amentoflavone from biflavones isolated from *autumnal Ginkgo biloba leaves*. Several studies have shown that amentoflavone binds to benzodiazepine receptors.

New skeletal flavonoids, anastatins A and B were isolated from the methanolic-extract of an Egyptian medicinal herb, the whole plants of *Anastaticahierochuntica*. Their flvonone structures having a benzofuran moiety were determined on the basis of chemical and physiochemical evidence. Anastatins A and B were found to show hepatoprotective effects on D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes and their activities were stronger than those of related flavonoids and commercial silybin[19].

Azorellacompacta, Azorellayareta and Laretiaacaulis (Apiaceae) are native species from the high Andes Mountains, northeastern Chile and they have been traditionally used to treat asthma, colds and bronchitis, illnesses with inflammation and pain as the main symptoms. It was proposed that these medicinal species contain bioactive compounds with anti-inflammatory and analgesic effects. In this context, azorellanol, 13-hydroxy-7-oxoazorellane and 7-deacetylazorellanol, three diterpenoids previously isolated only from these plants, were subjected to pharmacological and toxicological evaluation. Their torpical anti-inflammatory and analgesic activities along with acute toxicities or innocuousness were also investigated by Delpofte, and co-workers[20] and results indicate the absence of toxic and side effects in mice.

All compounds presented dose related inhibition of pain. 13-Hydroxy-7-oxoazorellane was the most potent analgesic but it was less effective than sodium -naproxen, the reference drug. Azorellanol exhibited the highest topical anti-inflammatory potency on AA (arachidonc acid) and TPA (12-deoxyphorbol 13tetradecanoate) induced edema and its effect was similar to the reference drugs like nimesulide and indomethacin. Probably, its mechanism of action could be explained through the inhibition of cyclooxygenase activity. Oxidative stress has been implicated in the etiology of a number of human ailments.

Hence, antioxidants especially derived from natural sources and capable of protecting against damage induced by reactive oxygen species (ROS) may have potential applications in prevention and/or cure of diseases. Indian medicinal plants provide a rich source of these potentially useful compounds. *Plumbagozeylanica* (known as ‘chitrak') and its constituents are credited with potential therapeutic properties including anti-atherogenic, cardiotonic, hepatoprotective and neuroprotective properties. Plumbagin (2- methyl-5-hydroxy, 4 naphthoquinone), isolated from the root of this plant was considered as the active ingredient.

Tilak and Co-workers[21] examined the possible antioxidant activity of plumbagin in relation to its reported beneficial properties, its ability to protect against oxidative damage in mitochondria during isolation. Mitochondria from rat liver, brain and heart were exposed to ROS generated by ascorbate-Fe^{2+}, H_2O_2-Fe^{2+} and the peroxyl radical generator, 2, 2'-azobis (2-methyl propionamide) dihydrochloride (AAPH). The parameters of damage assessed were products of lipid peroxidation, loss of mitochondrial enzyme and protein oxidation.

Indicate that plumbagin gave protection to different extents in the tissues. This can be ascribed to the presence of various amounts of substrates for oxidative reactions and- antioxidants/prooxidants in these tissue preparations. Their studies reveal that the differential ability (membrane protective properties) of plumbagin, in mitochondria, may be related to its radical scavenging abilities and that this antioxidant ability, may be at least in part, explain its potential therapeutic properties, Using Australian tea tree (Melaleuca alternifolia) as an example, terpenoid biogenetic pathways were found to be initiated at different stages of ontogeny. The cotyledon leaves of common terpinen-4-ol chemical variety seedlings were rich in α-pinene (7.4%), β-pinene (12.0%), and terpinolene (27.3%).

The non-common terpinolene variety was found to be rich in 1, 8-cineole (12.5%) and terpenolene (25.4%) and the 1, 8-cineole variety rich in 1, 8-cineole (37%) with significant quantities of α-pinene (15.5%), β-pinene (23.3%) and terpinolene (10.9%) reported by Southwell and Co-workers[22]

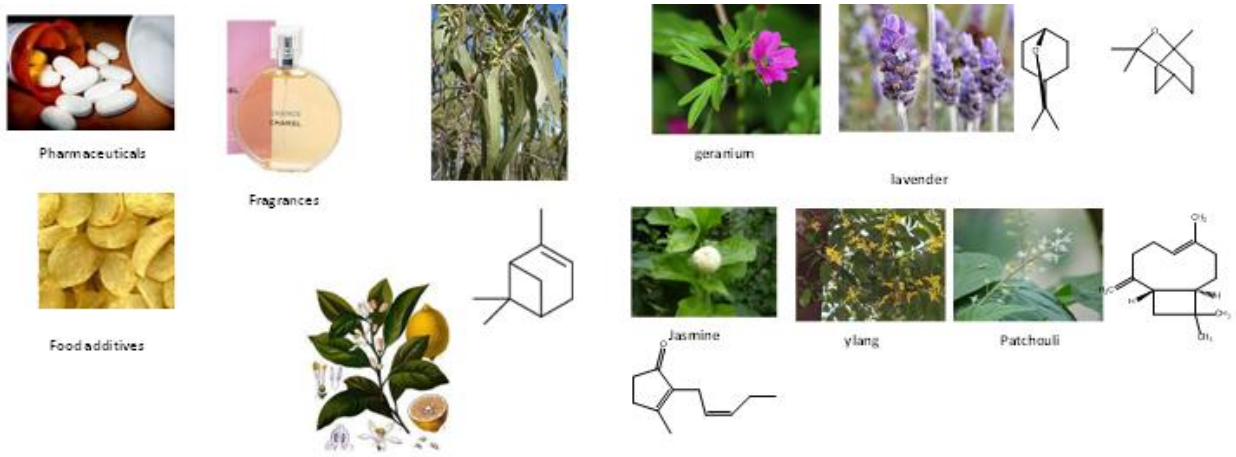

Figure 1: Secondary metabolites from Medicinal plants

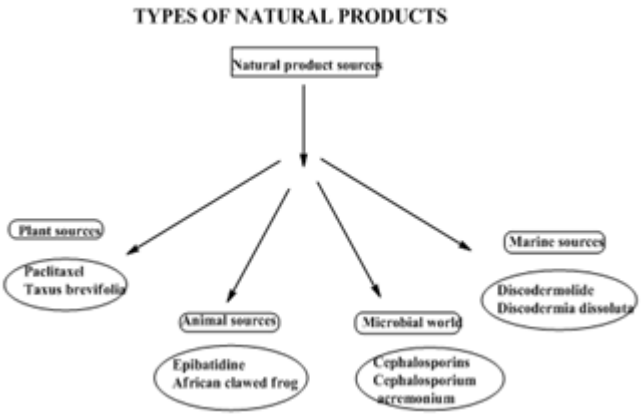

Figure 2: Natural products from Natural sources

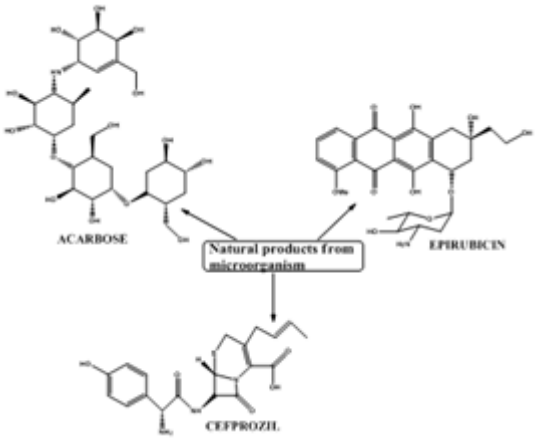

Figure 3: Natural products from micro organism

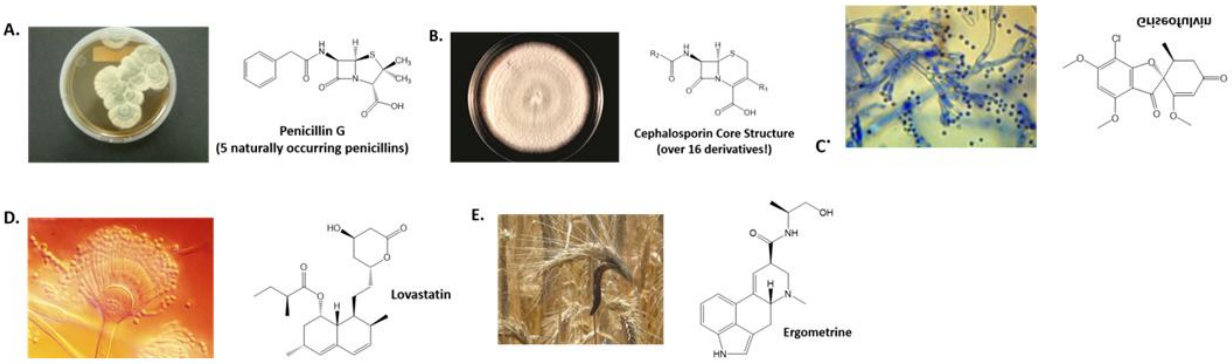

Figure 4: Examples of fungal secondary metabolites

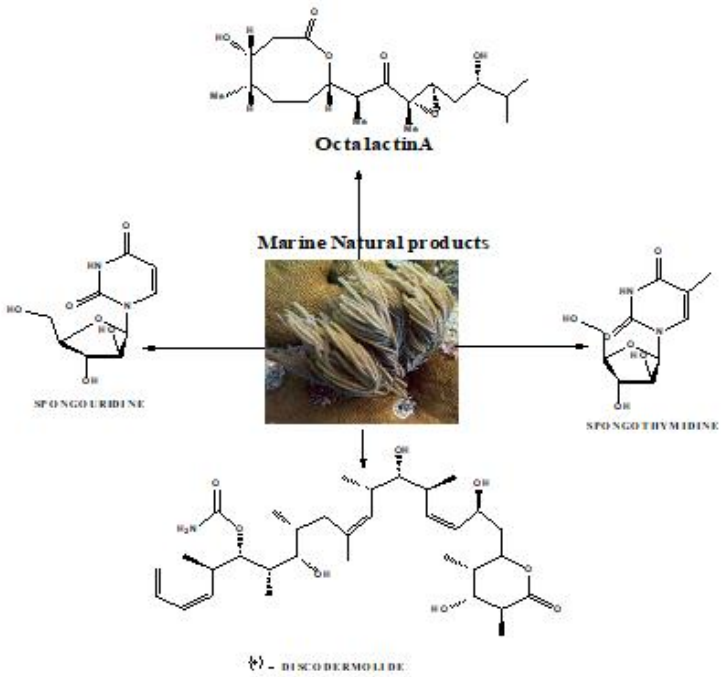

Figure 5: Natural products from Marine sources

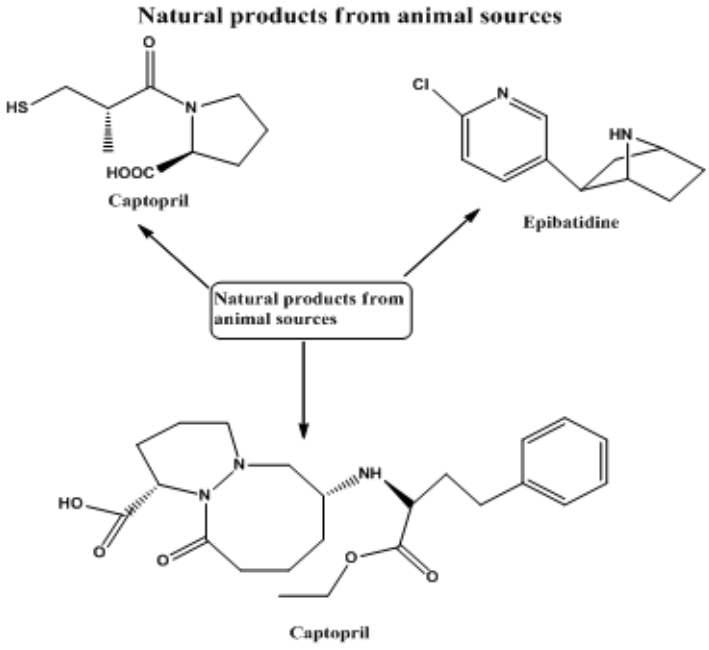

Figure 6: Natural products from Animal sources

1A.2. Anti-Cancer drugs from Plants:

Even though there are a large number of anticancer drugs in Market, there is a need for the availability of less toxic and more potent anticancer drugs. Most of the anti-cancer drugs even destroy the normal cells, because they are not selective. Natural products act as leads for various synthetically driven anticancer drugs available in the market. The first compound isolated was Podophylloforim, from the plant *Podophyllum peltatum*.[23]Etoposide and triposide are the modified analogs of Poelophyllotoin. These two analogs are used in the treatment of various cancers. It has indole alkaloids, which are having anticancer properties. This plant also contains ajmalicine an anti-hypertensive alkaloid. This plant is used as a remedy for diabetics [25]

An extract of the Pacific yew tree, *Taxusbrevifolia* was discovered to possess excellent anticancer properties in 1963, and its active component was isolated only a few years later in 1967 by Monroe Wall and his co-worker, MansukhWani.[26] They published their findings as well as the structure of the active component, paclitaxel (Taxol), [27] in 1971 Susan B. Horwitz, a molecular pharmacologist, established the novel mechanism of action of paclitaxel in 1979. Paclitaxel irreversibly binds to β-tubulin, thus promoting microtubule stabilization.[28] this tubulin-microtubule equilibrium is essential for cell multiplication, and its stabilization causes programmed cell death.[29] previously reported anticancer drugs, vinblastine, vincristine and podophyllotoxin also bind to tubulin, but prevent rather than promote microtubule formation. Paclitaxel was the first compound to be discovered to promote microtubule formation. It has been used in the treatment of several types of cancer, but most commonly for ovarian and breast cancers as well as non-small cell lung tumors. [30] It had sales of $750 million in 2002 and $1.0 billion in 2003.[31]Shortly after the discovery of paclitaxel and its unique mechanism, several compounds having the same mode of action were discovered. The epothilones, discovered from the myxo bacterium Sorangiumcellulosum, possess potential anticancer properties and show high in-*Vivo* activity, including activity against taxane-resistant cell lines. However, they exhibit moderate in-*Vitro* cytotoxicity[33]. Several semi-synthetic analogs of epothilones such as ixabepilone have been developed which are currently in Phase II clinical trials for treatment of breast cancer.

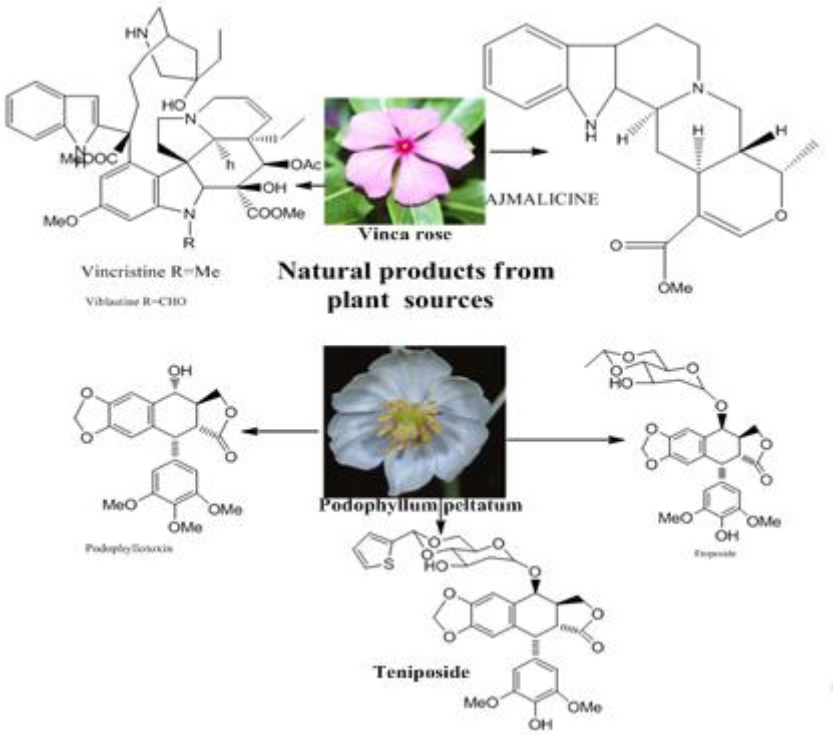

Figure 7: Natural products from Plant sources

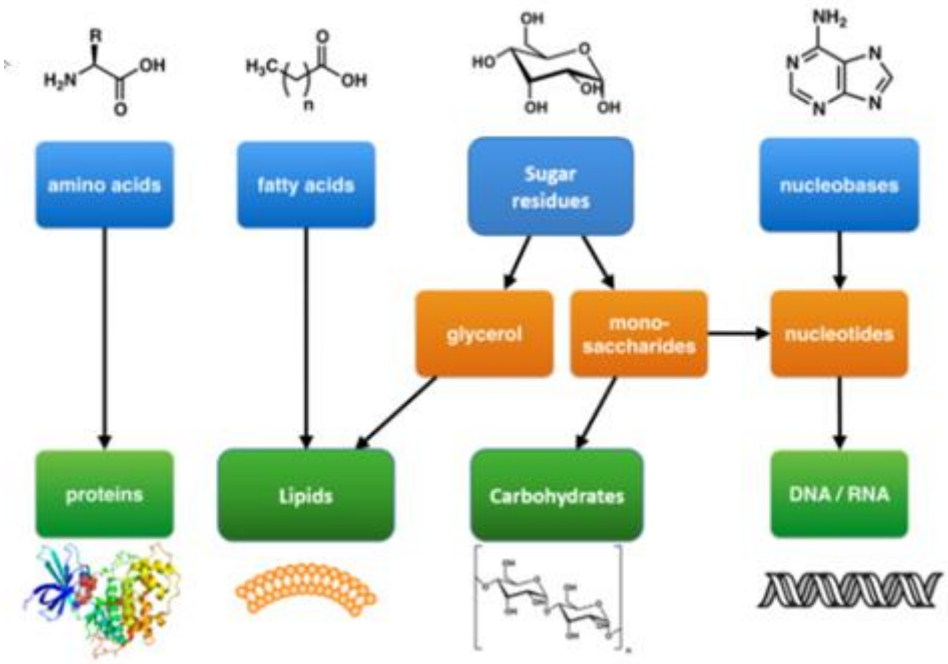

Figure 8: The Molecular building blocks of life are made from Organic compounds

Camptothecin, discovered from the deciduous tree *Camptothecaacuminata*, is also an anticancer agent which has a unique mechanism of action. Camptothecin and its derivatives are topoisomerase-I inhibitors, and cause cell death by DNA damage[34]. However, camptothecin itself is too insoluble to be used as a drug but its several water-soluble analogs, namely, topotecanandirinote can have been developed as effective drugs.[32]

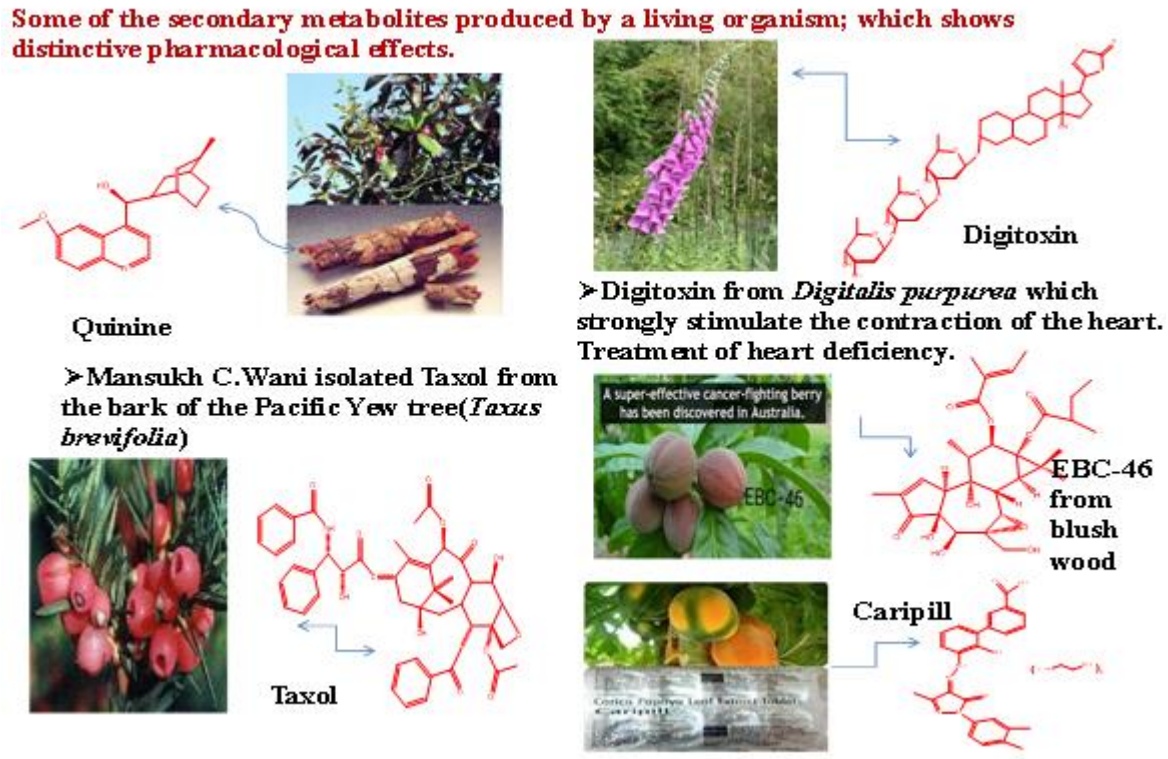

Figure 9: Quinine, Digitoxin, Taxol, Caripill from various Medicinal plants

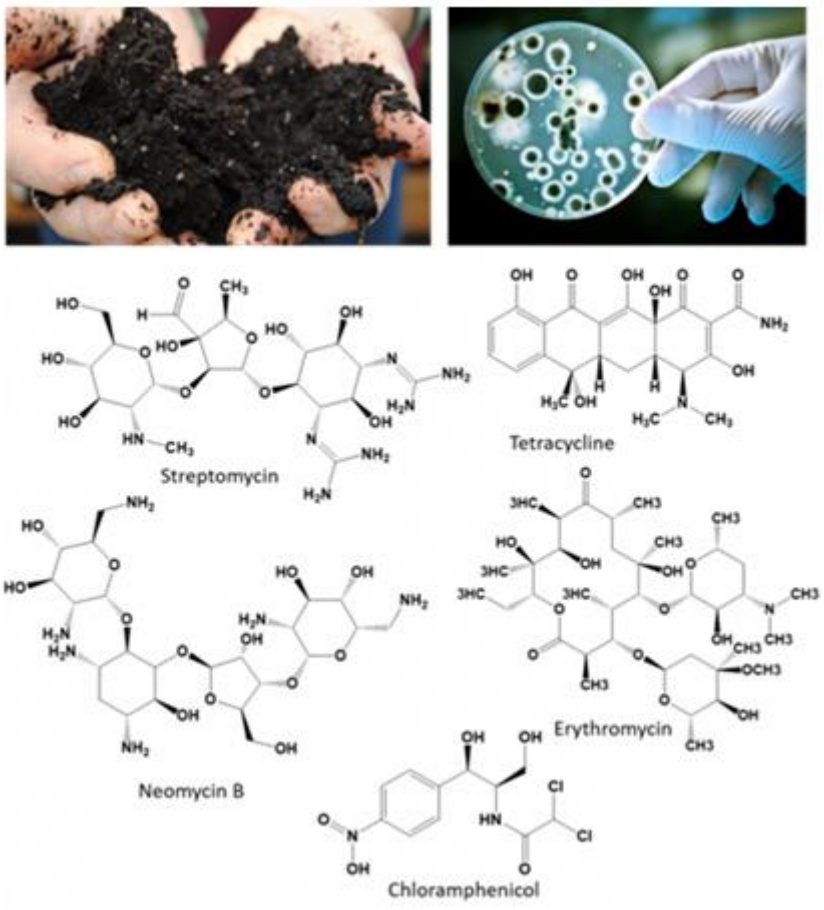

Figure 10: Bacteria isolated from soil are prolific producers of antibacterial compounds

Thus Natural resources and Natural products are still contributing to the entire medicinal world.

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