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RECENT ADVANCES IN THE NATURAL PRODUCTS DRUG DISCOVERY

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Abstract- Natural products isolated from plants, animals and microorganisms have made an important impact on curing the dreadful human diseases for example taxol, vinca alkaloids (vincristine and vinblastine), podophyllotoxin derivatives (etoposide, teniposide), camptothecin derivatives (topotecan and irinotecan) for cancer treatment; quinine and artemisinin for malaria treatment, captopril for hypertension treatment, premarin for induction of ovulation, pencillins, streptomycins, tetracyclines for the treatment of bacterial infections, Limitations to the wider therapeutic use of these natural products are: limited supply of the drugs from the natural sources, low yields, slow growth and sparsely distribution of the species, and commercially not viable total synthetic methods. For example Artemisnin isolated from the dried leaves and influorescences of *Artemisia annua* is the only drug for the treatment of malaria caused by the chloriquine resistant *Plasmodium falciparum*. The plant has lengthy growing cycle (12-18 months) to produce Artemisinin. The yield of Artemisnin could be around 5 Kg per 1000 Kg of dry leaves, which were produced from 1 ha of *A. annua* plantation. In 2004 an estimated 4700 ha *Artmesia* was grown all over the world. An estimated 17,000 ha are required to produce enough Artemisinin to manufacture 100 million adult treatments for year, where as the projection of global demand is 400 million ACT treatment per year. Similar problem exist with anticancer drug Taxol, which was produced by the Pacific Yew tree (*Taxus brevifolia*) and related Yew species. It takes roughly three trees to obtain a gram of pure Taxol and stripping the tree of it's bark, where most of the taxol is found, kills the Yew. The bark required to yield 1 kg of taxol is about 7000 kg. Although total synthesis of Taxol was achieved chemically using more than twenty steps and ended up with mg of synthetic Taxol and it is economically not at all viable. It is therefore essential to explore the alternative approaches and also to understand the biosynthesis of natural products. During the latter half of the twentieth century, investigations of biosynthetic pathways progressed from purely hypothetical speculation to studies of isotopically labelled precursors by whole cells or partially purified enzymes. To a lesser extent, these studies were complemented by the preparation of random mutants of fungi and actinomycetes and the identification of accumulated intermediates and shunt metabolites. Recent developments in the biotechnology, genetic engineering, synthetic biology (biosynthetic pathways, gene cluster identification, cloning of genes, recombinant DNA techniques, c-DNA) techniques, tissue culture and endophytes used in the production of important life saving drugs such as artemisnin, taxol, and other natural products including bioactive compounds in the form of neutraceuticals and dietary supplements will be discussed.
Keywords- Neutraceuticals, c-DNA, recombinant DNA techniques.

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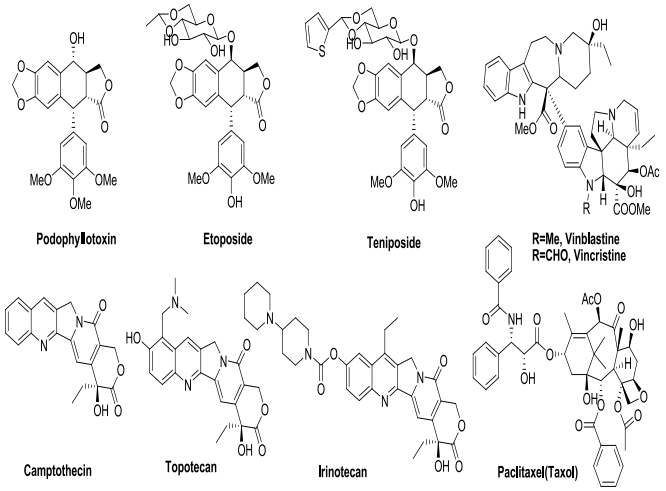
Introduction

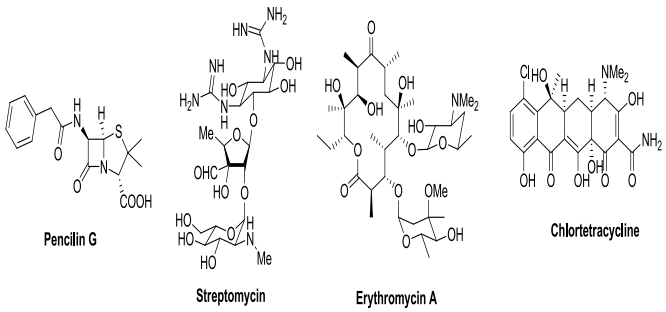
Indian medicinal system has a long history, and one of the oldest organized systems of medicine. It is mainly influenced by Ayurveda, Siddha, Unani and Homeopathy. These systems used natural products such as plant, terrestrial and marine animals, microorganisms derived preparations to cure the dreadful diseases. It was not until the early 1800's that the active principles from plants were isolated.

The history of natural products as anticancer agents has been started with discovery of podophyllotoxin from the *Podophyllum pelltatum*. Two derivatives of podophyllotoxin named etoposide and teniposide are in the market [1]. These compounds arrest cell

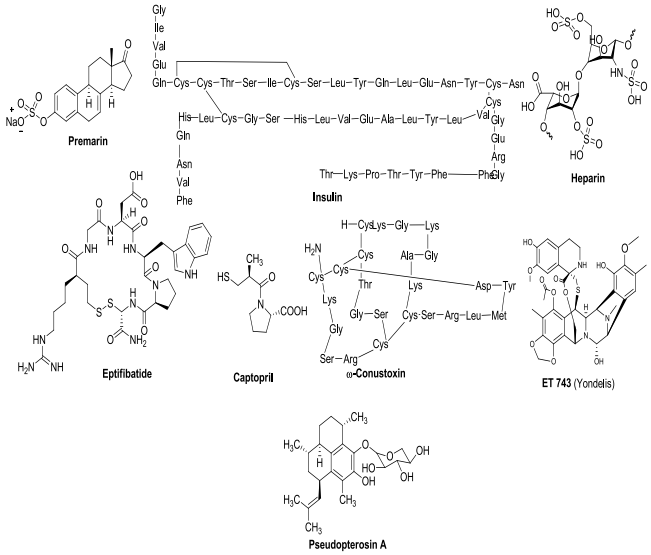
growth by inhibiting DNA topo-isomerase II, which causes double strand breaks in DNA. The plant *Catharanthus roseus* provided two vinca alkaloids i.e vincristine and vinblastine for the treatment of cancer [2]. Camptothecin (CPT) is a cytotoxic quinoline alkaloid which inhibits the DNA enzyme topoisomerase I (topo I). It was discovered in 1966 by M. E. Wall and M. C. Wani in systematic screening of natural products for anticancer drugs. It was isolated from the bark and stem of *Camptotheca acuminata*, a tree native in China. Two CPT analogues have been approved and are used in cancer chemotherapy today, topotecan and irinotecan [3]. Paclitaxel (taxol) isolated from the needles and bark of *Taxus brevefolia* is used in the treatment of lung, ovarian, and breast cancer [4].



Microorganisms played a very important role in the human health system by controlling various kinds of infections. The serendipitous discovery of Pencillin from the *Pencillium notatum* (fugus) by Alexander Fleming was the breakthrough, which opened the ways to carryout research work on the microorganism (bacteria and fungus) [5]. Subsequent work on this area lead to identify several antibiotics such as streptomycin [6], erythromycin [7], tetrcyclines [8] etc.

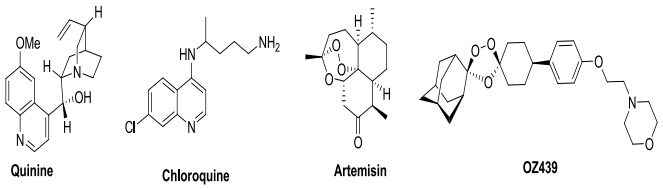


Certain animal (marine and terrestrial) derived compounds also played a very important role in the drug discovery. Premarin a derivative of estrogen isolated from the mare urine has been used to induce ovulation and hormone replacement therapy in human being [9]. Insulin [10] and heparin [11] isolated from the animals (porcine or bovine) have been used for antidiabetic and anticoagulating agents respectively. Eptifibatide is a cyclic heptapeptide derived from a protein found in the venom of the south-eastern pygmy rattlesnake [12]. Eptifibatide (Integrilin) is an antiplatelet drug that selectively blocks the platelet glycoprotein IIb/IIIa receptor. Captopril a peptide isolated from the pit viper (*Bothrops jararaca*) venom [13]. Captopril is an angiotensin-converting enzyme inhibitor (ACE inhibitor) used for the treatment of hypertension and some types of congestive heart failures. A systematic research on marine animals began around 50 years back, which resulted in discovering three marine drugs such as Conus toxin (Prialt) from the *Conus magus* (Conus snail) approved for the chronic pain [14], ET 743 (Yondelis) [15] from the ascidian (*Ecteinascidia turbinate*) for cancer and pseudoptorosin A [16] from the gorgonian (*Pseudopterogorgia elisabethae*) for antiinflammation.



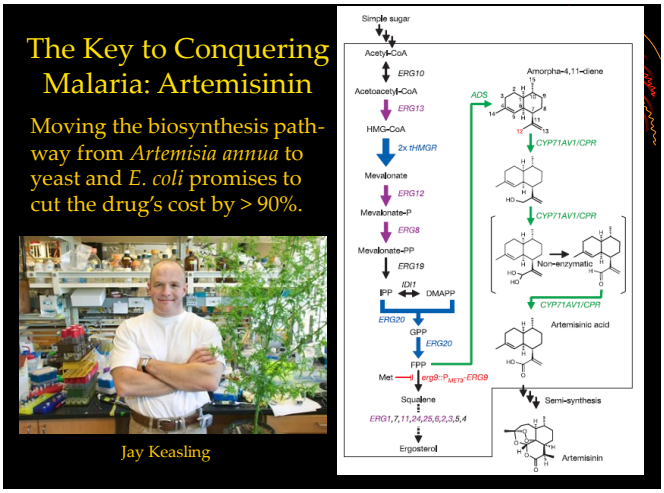
Natural products not only served as drugs to treat various human ailments, they also played a very important role as template to develop synthetic drugs. For example quinine [17] isolated from the bark of Cinchona (*Cinchona officinalis*) was the only drug to cure the malarial fevers before world wars. Bayers laboratory developed the antimalarial agent Chloroquine [18] on the basis of structural information obtained from quinine, which was introduced into market in the year 1947. Resistance has been emerged recently for chloroquine and it is no more effective to curing malaria in few patients. Nature has provided another antimalarial agent to solve this problem. The Chinese group developed artemisinin from the leaves and inflorescence of *Artemisia annua* [19]. Artemisinin is a sesquiterpene lactone containing an unusual peroxide bridge, which is believed to be responsible for the antimalarial activity. The plant has lengthy growing cycle (12-18 months) to produce artemisinin. The yield of artemisnin could be around 5 Kg per 1000 Kg of dry leaves, which were produced from 1 ha of *A. annua* plantation. In 2004 an estimated 4700 ha *Artmesia* was grown all over the world. An estimated 17,000 ha are required to produce enough artemisinin to manufacture 100 million adult treatments for year, whereas the projection of global demand is 400 million ACT treatment per year. Similar problem exist with anticancer drug taxol, which was produced by the Pacific Yew tree (*Taxus brevifolia*) and related Yew species. It takes roughly three trees to obtain a gram of pure taxol and stripping the bark, where most of the taxol is found, kills the Yew. The bark required to yield 1 kg of taxol is about 7000 kg. Although total synthesis of taxol was achieved chemically using more than twenty steps and ended up

with mg of synthetic taxol and it is economically not at all viable [20]. The synthetic artemisinin has also been achieved in the laboratory, however it is also not economically viable [21]. Since the pharmacopore is well defined as peroxide in the artemisinin several research groups all over the world are engaged to develop simplified compound with peroxide skeleton. As a result a novel synthetic peroxide antimalarial drug candidate, OZ439[22] has successfully completed Phase 1 clinical trials where it was shown to be safe developed by Medicines for Malaria Venture (MMV) in partnership with three academic institutes: University of Nebraska Medical Center, USA, Monash University, Victoria, Australia, and the Swiss Tropical and Public Health Institute.



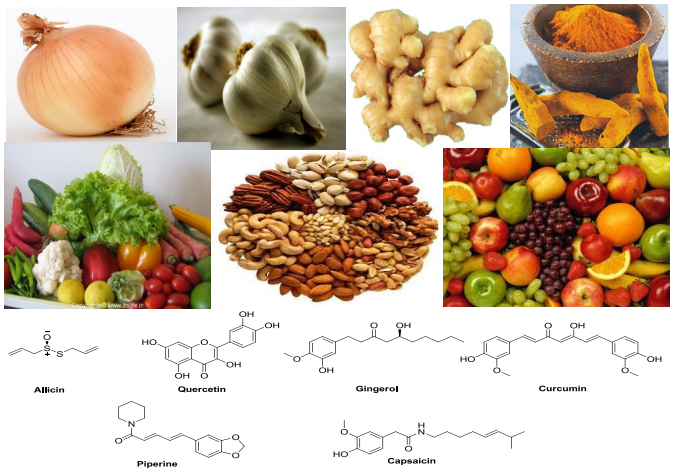
It is therefore essential to explore the alternative approaches and also to understand the biosynthesis of natural products. During the latter half of the twentieth century, investigations of biosynthetic pathways progressed from purely hypothetical speculation to studies of isotopically labelled precursors by whole cells or partially purified enzymes. To a lesser extent, these studies were complemented by the preparation of mutants of fungi and actinomycetes and the identification of accumulated intermediates and metabolites. Recent developments in the biotechnology, genetic engineering, synthetic biology (biosynthetic pathways, gene cluster identification, cloning of genes, recombinant DNA, c-DNA) techniques, tissue culture used in the production of important therauputic drugs such as artemisnin, taxol, and other natural products. In 2006, a team from UC Berkeley reported that they had engineered *Saccharomyces cerevisiae* yeast to produce the precursor artemisinic acid. The synthesized artemisinic acid can then be transported out, purified and chemically converted into artemisinin that they claim will cost roughly 0.25 cents per dose. In this effort of synthetic biology, a modified mevalonate pathway was used, and the yeast cells were engineered to express the enzyme amorphadiene synthase and a cytochrome P450 monooxygenase (CYP71AV1), both from *A. annua*. A three-step oxidation of amorpha-4,11-diene gives the resulting artemisinic acid. Amyris Inc. collaborated with UC Berkeley and the Institute for One World Health to further develop this technology. The collaboration, known as the Artemisinin Project, is supported by funding from the Bill & Melinda Gates Foundation, and aims to create a source of nonseasonal, high-quality and affordable artemisinin to supplement the botanical supply [23]. Few research groups are also exploring to produce these life saving drugs from the endophytes.

Natural products also currently playing a very important role in the neutracetucal industry. The ingredients we use in our daily food have got immense medicinal importance. For example in Indian population we use onions, garlic, ginger, turmeric in the preparation of curries and other food preparations. Thanks to our ancestors and ayurveda system for providing healthcare system for us. Recent studies on onions indicated its beneficial effect in cough, cold, asthma, bronchitis, cancers etc. The WHO supports the use of onion for these disease. Onions (*Allium cepa*) are rich source for sulphur containing compounds and quercetin- both being strong antioxidants. These compounds have a variety of health-functional properties, including anticancer and antimicrobial activities. Garlic (*Allium sativum*) also a very rich source of sulphur compounds. Allicin is an organosulfur compound obtained from garlic. Several animal studies published indicate that allicin may reduce atherosclerosis and fat deposition, normalize the lipoprotein balance, decrease blood pressure, have anti-thrombotic and anti-inflammatory activities, and function as an antioxidant to some extent. Gingerol is one of the active constituents of ginger (*Zingiber officinale*) has been investigated for its effect on various cancerous tissues. Gingerol seems to be effective in an animal model of rheumatoid arthritis. Turmeric (*Curcuma longa*) is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae. *In vitro* and animal studies have proven that curcumin has antitumor, antioxidant, antiarthritic, antiamyloid, anti-ischemic, and anti-inflammatory properties. In addition it may be effective in treating malaria, prevention of cervical cancer, and may interfere with the replication of the human immunodeficiency virus (HIV). Dietary piperine obtained from the black pepper (*Piper nigrum*) by favorably stimulating the digestive enzymes of pancreas, enhances the digestive capacity and significantly reduces the gastrointestinal food transit time. Piperine has been demonstrated in *in vitro* studies to protect against oxidative damage by inhibiting or quenching free radicals and reactive oxygen species. Black pepper or piperine treatment has also been evidenced to lower lipid peroxidation in vivo and beneficially influence cellular thiol status, antioxidant molecules and antioxidant enzymes in a number of experimental situations of oxidative stress. Capsaicin isolated from the fruits of *Capsicum frutescens* (red chilly) is used in diabetic neuropathy. Capsaicin affects all the small unmyelinated nerve endings in the nervous system of animals. Research also showed that capsaicin lowers the blood glucose in antidiabetic studies.



The spices, vegetables, nuts and fruits consumed by Indian population all have some or other medicinal importance. The western world has realized the importance of Indian medicinal system and currently introducing into their medicinal system. The FDA of United States relaxed norms to promote the usage of these products in the form of nutraceuticals. Nutraceutical (nutrition and pharma-

ceutical) is a food or food product that provides health and medical benefits, and in the prevention disease. Nearly two-thirds of the American population takes at least one type of nutraceutical health product. The use of nutraceuticals is believed to be an attempt to get the desirable therapeutic effect with reduced side effects as compared with other allopathic drugs. The nutraceutical industry in the US is about $86 billion. This figure is slightly higher in Europe and, in Japan. 47% of the Japanese population consume nutraceuticals.



Several herbal companies in India making the herbal crude extracts and fractions from the spices, vegetables, nuts, fruits and medicinal plants and exporting to Europe and America as dietary supplements. A dietary supplement is a product that contains nutrients derived from food products that are concentrated in liquid or capsule form. A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The dietary ingredients include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or fractions of plants or animals or microorganisms, and may be found in many forms such as tablets, capsules, soft-gels, liquids, or powders. Dietary supplements do not have to be approved by the U.S. Food and Drug Administration (FDA) before marketing. Although supplements claim to provide health benefits, products usually include a label that says: “These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”

Conclusion

In conclusion natural products obtained from the plants, animals, microorganisms played a very important role in medicinal systems of various civilizations all over the globe. The natural products not only served as drugs and also templates to develop several synthetic drugs. The limitations such as scarcity of material, yield of compound and uneconomical synthetic drugs led to identify the alternative methods. As a result focus has been shifted on biotechnology tools, genetic engineering and synthetic biology to produce the bioactive compounds from engineered microorganisms. The Western world has realized the importance of Indian medicinal system consequently the global demand for natural products in the form neutraceuticals, dietary supplements and functional foods is growing up all over the world, which is good sign for Indian herbal industry.

References

[1] Gordaliza M., Castro M.A., Miguel del Corral J.M., San Feliciano A. (2000) *Curr. Pharm. Design*, 6, 1811.
[2] Alejandro Donoso J., Green Louis S., Irene E., Heller-Bettinger (1977) *Cancer Res.,* 37,1401.
[3] Wall M. and Wanl M. (1996) *Annals of the New York Academy of Sciences,* 803, 1.
[4] Wani M., Taylor H., Wall M., Coggon P., McPhail A. (1971) *J. Am. Chem. Soc.,* 9, 2325.
[5] MacFarlane G., Alexander Fleming (1984) *The Man and the Myth*.
[6] Schatz A., Waksman S.A. (1944) *Soc. Exptl. Biol. & Med*, 57, 244.
[7] McGuire J.M., Bunch R.L., Anderson R.C., Boaz H.E., Flynn E.H., Powell M., Smith J.W. (1952) *Antibiot. Chemother.,* 2, 281.
[8] Chopra I. and Roberts M. (2001) *Microbiol. Mol. Biol. Rev.,* 65, 232.
[9] Graham A., Colditz (2005) *Clin. Cancer Res,* 11, 909.
[10] Kotzke G., Schütt M., Missler U., Moller D.E., Fehm H.L., Klein H.H. (1995), 38, 757.
[11] Barbara A., Konkle., Thomas L., Bauer, Gowthami A., Douglas B. (2001) Cines *Ann Thorac Surg.,* 71, 1920.
[12] Scarborough R.M. (1999) *Am. Heart J.,* 138, 1093.
[13] Charles G., Smith., John R.V. (2003) *The FASEB Journal,* 17, 788.
[14] Wermeling D.P. (2005) *Pharmacotherapy*, 25, 1084.
[15] Patel R.M. (2011) *Internat. J. Curr. Pharmaceut. Res.,* 3, 65.
[16] Sally A.L., William F., Gayle K.M.M., Clardy J.J. (1986) *Org. Chem.,* 51, 5140.
[17] Jane A., Ambrose O.T.S., Annette E., Adoke Y., James K.T.R., Frederick N.B., Philip J., Umberto D.A. (2011) *Malaria Journal*, 10,144.
[18] Stanislav R. (1996) *Arch. Pham. Pharm. Med. Chem.,* 329, 115-119.
[19] Fulong L. (2009) *Molecules,* 14, 5362.
[20] Nicolaou K.C., Yang Z., Liu J.J., Ueno H., Nantermet P.G., Guy R.K., Claiborne C.F., Renaud J. (1994) *Nature*, 367, 630-634.
[21] Yadav J.S., Satheesh Babu R. and Sabitha G. (2003) *ARKIVOC*, iii, 125-139.
[22] Susan A.C., Sarah A.B., Ian C.B., Reto B., Michaelv C. (2011) *PNAS,* 108, 4400.
[23] Dae-Kyun R., Eric M.P., Mario O., Karl J.F., Karyn L.N., John M.N., Kimberly A.H., Rachel A.E., Timothy S.H., James K., Michelle C.Y.C., Sydnor T.W., Yoichiro S., Richmond S., Jay D.K. (2006) *Nature*, 440, 940.