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Chemical Diversity in Nature Produces Potent Drugs of Various Ailments; Natural Products

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Abstract: Nature is a unique source of structures of high phytochemical diversity, many of them possessing interesting pharmacological activities and medicinal properties. Many important substances were obtained anciently, e.g. foodstuffs, building materials, dyes and other extracts from nature. Natural products remain a prominent source for the discovery of new drugs and drug leads even from Vedic period. Population growth insufficient supply of drugs, prohibitive cost of treatments, side effects of allopathic drugs and development of resistance to currently used drugs for infectious diseases have increased attention on plant materials as a source of medicines for a wide variety of health disease.

Keywords: Natural products, Chemical diversity, Drug discovery, potent drugs in nature.

I. INTRODUCTION

Nature is having very broad meaning which includes natural, physical or material world or universe. "Nature" refers to the phenomena of the physical world, and also to life in general. It ranges in scale from the subatomic to the cosmic.

The word nature is derived from the Latin word natura, or "essential qualities, innate disposition", and in ancient times, literally meant "birth" [1]. Natura was a Latin translation of the Greek word physis, which originally related to the intrinsic characteristics that plants, animals and other features of the world develop of their own accord [2]. The concept of nature in holistic manner is one of several expansions of the original notion; it began with certain core applications of the word physis by pre-socratic philosophers and has steadily gained currency ever since.

In today's scenario, "nature" often refers to geology and wildlife. Nature may be called as general realm of various types of animals and living plants, and in some cases to the processes associated with inanimate objects – the way that things exists on their own and make their own changes, such as the weather and geology of the Earth and the matter and energy of which all these things are composed. Natural environment often considered as wild animals, rocks, forest, beaches, and in general those things that have not been substantially changed by human intervention or which persist despite human intervention. For example, manufactured objects and human interaction generally are not considered part of nature, unless qualified as, for example, "human nature" or "the whole of nature".

II. GLOBAL HEALTH AND NATURE

Natural environment is a key determiner of health. A report published by the World Health Organization claims that 'approximately one-quarter of the global disease burden and more than one-third of the burden among children, is due to modifiable environmental factors'. However, WHO has focused much on environmental degradation which includes the amount of death and disease caused by factors such as unsafe drinking-water and sanitation, and indoor and outdoor air pollution, and paid very little attention to the impacts of environmental deprivation. The same focus is reflected more broadly within 'environmental health' as a discipline and a profession.

Health is most valued asset for every human being. Basically, all people have it in their 'top three' priorities. In the 5th Century B.C., a Greek statesman by the name of Pericles stated that 'Health is that state of moral, mental, and physical wellbeing that enables a person to face any crisis in life with the utmost grace and facility' [3]. However, the factors that enhance health have been discovered in the latter half of the 20th Century through various researches. Recent theories of disease have revealed that now diseases have no more single cause explanations but multiple ones are there in which behavioral, environmental, biological and genetic factors all taken into account [4].

The World Health Organization (WHO) states health is 'A state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity'. The word 'health' is derived from the Greek word 'hal' or whole. It is this holistic perspective of health which has emerged in the last 50 years. However, it is simply not possible to achieve the WHO goal. Rene Dubos stated, 'The concept of perfect and positive health is a utopian creation of the human mind. It cannot become reality because man will never be so perfectly adapted to his environment...It is true that the modern ways of life are creating disease that either did not exist



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a few decades ago or are now more common than in the past...The utopia of positive health constitutes a creative force because like other ideals, it sets goals and helps medical science to chart its course towards them' [5].

Nature always stands as a golden mark to exemplify the outstanding phenomenon of symbiosis. Nature has provided valuable materials for the benefits of human kind. The knowledge of drug has accumulated over thousands of years as a result of man's inquisitive nature so that today we possess many effective means of ensuring health care [6].

Health, wellness and economic growth are important in the development of a people. To the vast majority of people especially in all developing countries, health means much more than the mere absence of disease [7]. It is mostly prayed but rarely achieved. Health is state when there is perfect harmony between humans and their environment.

III. ROLE OF HERBAL MEDICINES IN TRADITIONAL HEALING

The pharmacological treatment of disease with the use of herbs began long ago [8]. Methods of traditional healing throughout the world have commonly used herbs as part of their tradition. Some of these traditions are briefly described below, with some examples of important healing practices around the world that used herbs for this purpose.

A. Traditional Chinese Medicine

Traditional Chinese medicine has been used by Chinese people from ancient times. Although various sources like animal and mineral materials have been used, the primary source of mitigation is botanical. Of the more than 12, 000 items used by traditional healers, about 500 are in common use. These traditional healing products are used only after some kind of processing, which may include stirfrying or soaking in vinegar or wine. In China use of traditional medicines is very common, even half of the population regularly uses traditional remedies, with the highest prevalence of use in rural areas. About 5000 traditional remedies are available in China; they account for approximately one fifth of the entire Chinese pharmaceutical market [9].

B. Japanese traditional medicine

Many herbal remedies found their way from China into the Japanese systems of traditional healing. Herbs native to Japan were classified in the first pharmacopoeia of Japanese traditional medicine in the ninth century [10].

C. Indian Traditional Medicine

Ayurveda is a traditional medical system prevalent in India that has been known for nearly 5000 years. It includes diet and herbal remedies, while emphasizing the body, mind and spirit in disease prevention and treatment [11].

IV. INDIAN SYSTEM OF MEDICINE: AYURVEDIC CONCEPT OF HEALTH

Ayurveda is the oldest existing health care system, originating in the ancient Vedic civilization of India. Health is defined as the state of equilibrium of dosha (humours), agni (digestive juices, enzymes and hormones) dhatu (tissues) and the normal excretion of mala(waste materials), along with a happy state of atma (soul), indriya (sensory and motor organs), and manas (mind). Ayurveda is a Sanskrit derived from ayuh (life) and veda (knowledge) and is also known as the science of long life. It is 5,000-year-old system of Indian medicine (1500–1000BC).

According to Ayurveda, each person will be influenced by certain elements more than others. This is because of their prakriti, or natural constitution. Ayurveda categorizes the different constitutions into three different doshas:

- A. Vata dosha, in which the air and space elements dominate.
- *B.* Pitta dosha, in which the fire element dominates.
- C. Kapha dosha, in which the earth and water elements dominate [12].

The fundamental object of Ayurvedic therapy is to make balance between these three major body systems. The balanced coordination of body, mind and consciousness is Ayurvedic definition of health. About 8,000 herbal remedies have been codified in Ayurveda. The Rigveda (5000 BC) has recorded 67 medicinal plants, Yajurveda 81 species, Atharvaveda (4500-2500 BC) 290 species, Charak Samhita (700 BC) and Sushrut Samhita(200 BC) had described properties and uses of 1100 and 1270 species respectively, these are still used in the classical formulations, in the Ayurvedic system of medicine [13] [14].

Some important herbs in Ayurveda are Rauwolfia serpentita, Asparagus racemosus, Alstonia scholaries, Anacardium occidentale, Anona squamosa ,Aristolochia indica, Withania somnifera, Rubia cordifolia, Saussurea lappa ,Saraca indica,Semecarpus anacardium, Tylophora asthmatica, Vinca rosea etc.

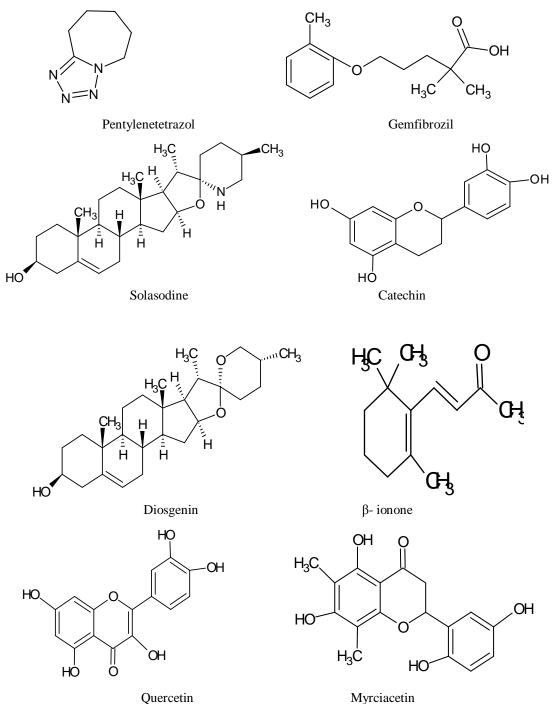


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V. THE ROLE OF PLANT TO HUMAN HEALTH

Herbs and human health can never be separated. Herbs are essential for good health. However, there are many herbs, which have medicinal values due to presence of certain enzymes, amino acid, alkaloids, steroids and vitamins etc.

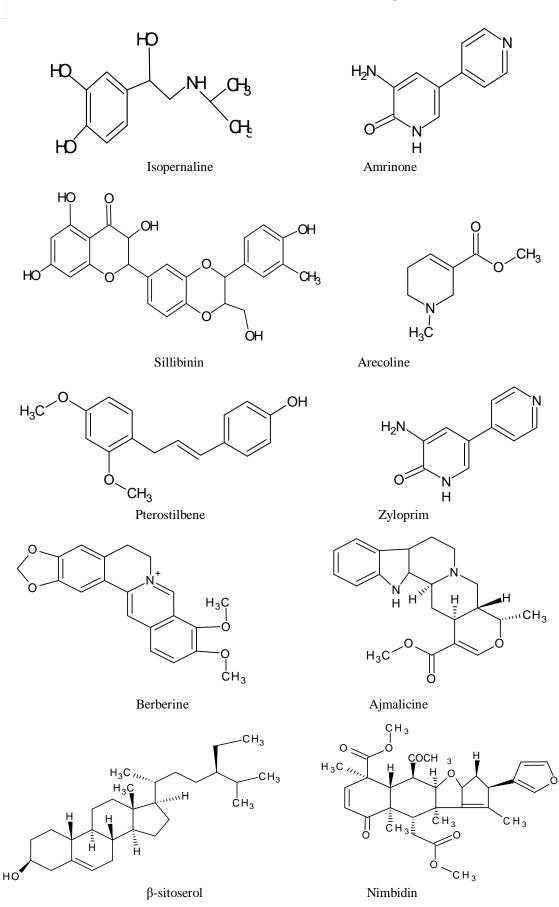
Medicinal plants are the most essential source of life saving drugs for the majority of the world's population. Currently extracted bioactive compounds from plants are used as food additives, pigments, dyes, insecticides, cosmetics and perfumes and fine chemicals. These compounds belong to a group known as secondary metabolites [15]. A study on plant secondary metabolites has been increasing last 50 years. The molecules are known to play a major role in the adaptation of plants to their environment, but also an important source of pharmaceutical [16] [17].



VI. STRUCTURES OF THE REPRESENTATIVE DRUGS OBTAINED FROM PLANTS

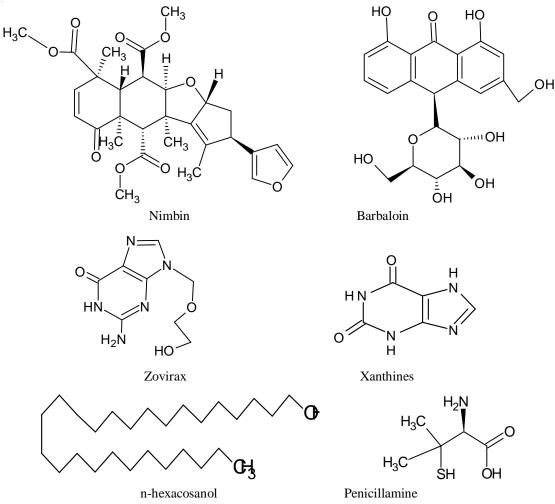


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VII.SIGNIFICANCE OF MEDICINAL PLANTS TO HUMAN BEING

Use of plants as a source of medicine has been inherited and significant component of the health care system in India. The plants have been used for defense, protection and nourishment by human being. Many of the modern medicines are produced indirectly from medicinal plants. Plants are directly used as medicines by a majority of cultures around the world, for example Chinese medicine and Indian medicine. Many food crops have medicinal effects and are resources of new drugs. It is estimated there are more than 250, 000 flower plant species. Studying medicinal plants helps to understand plant toxicity and protect human and animals from natural poisons. Cultivation and preservation of medicinal plants protect biological diversity.

Medicinal plants have many characteristics when used as a treatment, as follow:

- A. Synergic medicine- The ingredients of plants all interact so their uses can complement or damage others or neutralize their possible negative effects.
- *B.* Support of official medicine- In the treatment of complex cases like cancer diseases the components of the plants proved to be very effective.
- *C.* Preventive medicine- It has been proven that the component of the plants also characterize by their ability to prevent the appearance of some diseases. This will help to reduce the use of the chemical remedies which will be used when the disease is already present [18]

VIII. NATURAL PRODUCTS: THE INHERENT POTENTIALITY

Products of natural origins can be called "natural products." A natural product is a chemical compound or substance produced by living organisms found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design [19].



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The studies of natural products are very important because of so many reasons. They include:

- A. Natural products are the source of the most complex and fascinating chemical structures.
- B. Natural products represent biological diversity.
- C. Natural products are expressions of the genome.
- D. Natural products represent natural biological activity, whether as single compounds or as complex mixtures.
- *E.* Natural products are part of the natural wealth of the country, and can be an important source of livelihood, from agriculture and food, pharmaceuticals, fine chemicals industry.

Natural products can be an effective bridge from tradition to modern scientific developments, including genetics, molecular biology, biotechnology, and pharmaceutical science.

IX. TYPES OF NATURAL PRODUCTS

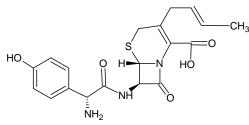
Natural products include

- A. An entire organism that has not been subjected to any kind of processing or treatment than a simple process of preservation
- B. Part of an organism (e.g., leaves or flowers of a plant).
- C. An extract of an organism or part of an organism.
- *D*. Pure compounds (e.g., alkaloids, coumarins, flavonoids, glycosides, lignans, steroids, sugars, terpenoids, etc.) isolated from plants, animals or microorganisms [20]. Secondary metabolism include products of overflow metabolism as a result of nutrient limitation, shunt metabolism produced during idiophase, defense mechanism regulator molecules, etc [21].

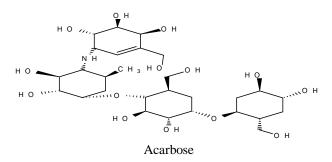
In most cases the natural products refer to secondary metabolites, small molecules produced by an organism that are not necessary for the survival of the organism. Natural products can be from any terrestrial or marine source: plants (e.g., Taxol from *Taxus brevifolia*), animals (e.g., vitamins A and D from cod liver oil), or microorganisms (e.g., doxorubicin from *Streptomyces peucetius*). Several drugs are derived from various naturally occurring medicinal sources. These can be divided into following categories:

X. NATURAL PRODUCTS FROM MICROORGANISMS

Microorganisms such as bacteria and fungi have been invaluable source for new drugs. These microorganisms produce a large variety of antimicrobial agents. Microorganisms as a source of drug were not explored until the discovery of penicillin in 1929 by Fleming from the fungus *Penicillium notatum*. The discovery of this revolutionary drug prompted the investigation of nature for other novel compounds. A large number of terrestrial and marine microorganisms have been screened for drug discovery. Microorganisms have a wide variety of potentially active substances and have led to the discovery of antibacterial agents like cephalosporins antidiabetic agents like acarbose [22].



Cefprozil (cephalosporin)



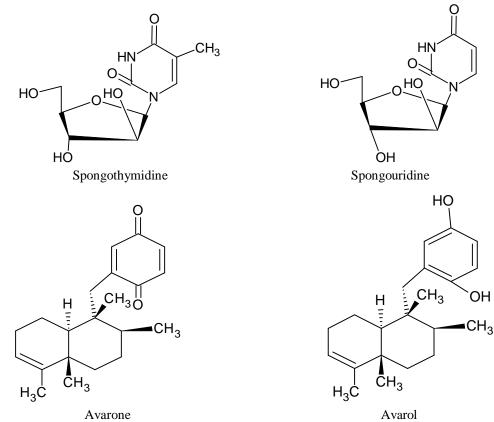


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XI. NATURAL PRODUCTS FROM MARINE ORGANISMS

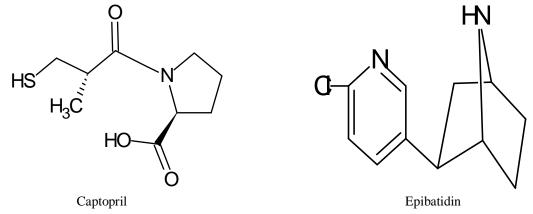
Spongouridine and spongothymidine were the first active compounds to be isolated from marine species. These compounds show great potential as anticancer and antiviral agents. Their discovery increased extensive research to identify new drug from marine organisms. About 70% of the earth's surface is covered by the oceans, providing biodiversity for drug sources many marine organisms have a sedentary lifestyle and thereby synthesize many complex and extremely potent chemicals [23].

Avarone and avarol isolated from the sponge *Dysidea avara* showed anti-HIV activity, but controlled studies failed to confirm their utility in treatment of HIV-infection. Illimaquinone isolated from red sea sponge Smenospongia sp. inhibited specifically RNase H[24].



XII.NATURAL PRODUCTS FROM ANIMAL SOURCES

Animals have also been a source of new lead compounds. Epibatidine obtained from the skin of an Ecuadorian poison frog, is ten times more potent than morphine [25]. Venoms and toxins from animals have played a pivotal role in designing a multitude of cures for several ailments. They have proved important tools in studying receptor, ion channel and enzymes. For example, Teprotide a peptide isolated from the venoms of a Brazilian viper, has led to the development of antihypertensive agents cilazapril and captopril.

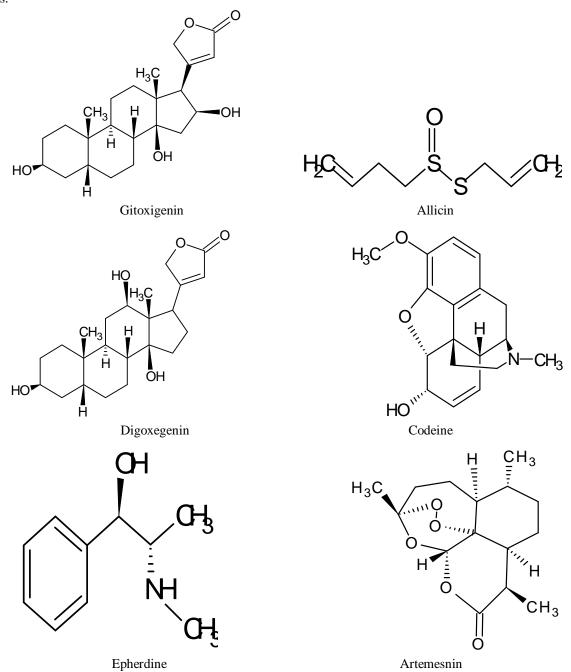




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A. Natural Products from Plant Sources

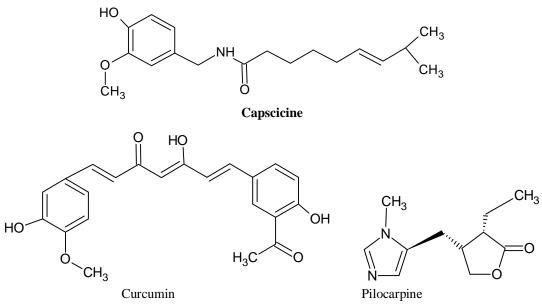
There is a worldwide green revolution which is reflected in the belief that herbal remedies are safer and less damaging to the human body than synthetic drugs. Many important drugs in the use today were derived from plants or from starting molecules of plant origin. Plant products are important gift of nature to us. Plants produce variety of natural products with highly diverse structures. The use of plants as medicines has a long history in the treatment of various diseases. The earliest known records for the use of plants from Mesopotamia in 2600 B.C. [26] To date 35,000-70,000 plant species have been screened for their medicinal use [27]. Plants provide a large bank of rich, complex and highly varied structures which are unlikely to be synthesized in laboratories. Some of the useful plant drugs include vinblastine, vincristine, taxol, podophyllotoxin, camptothecin, digitoxigenin, gitoxigenin, digoxigenin, tubocurarine, morphine, codeine, aspirin, atropine, pilocarpine, capscicine, allicin, curcumin, artemesinin and ephedrine among others.





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XIII. NATURAL PRODUCT AS MEDICINALLY USEFUL AGENTS

Natural product chemistry stems from the use of nature for medicinal purposes. The importance of plant in the management of human health cannot be over-emphasized. Furthermore, the active components of herbal remedies have the advantage of being combined with many other substances that appear to be inactive. However, these complementary components give the plant as a whole a safety and efficiency much superior to that of its isolated and pure active components.

The natural products today symbolise safety in contrast to the synthetics that are unsafe to human health and environment. Natural products still play a very dominant role in the medicine of the remaining 20% of the world's population. Between 1983 and 1994 41% of new approved drugs have natural products as their main source.

The isolation and characterization of biologically active compounds from natural sources is called pharmacognosy. There are three main areas of inquiry in Pharmacognosy.

- A. Extraction
- B. Biological evaluation of extracts.
- C. Isolation/characterization of active principles of the extracts.

Pharmacognosy differs from the more basic form of natural products chemistry, phytochemistry, which focuses only on extraction, isolation and characterization of compounds that may serve as taxonomic markers.

The importance of natural product in this regard can be analyzed using three criteria;

- 1) The rate of introduction of new chemical entities of wide structural diversity, including serving as templates for semi synthetic modification.
- 2) The number of diseases prevented by these substances.
- 3) Their frequency of use in the treatment of disease.

The study of natural products has had a number of advantages. It has led to the discovery of a variety of useful drugs for the treatment of diverse diseases and contributed to the development of separation science and technology, spectroscopic methods of structure elucidation and synthetic methodologies that now make up the basics of analytical organic chemistry. Currently, at least 119 chemical substances derived from 90 plant species can be considered important drugs that are in use in one or more countries [28].

These few accounts underscore not only the potential of natural products as a source of drugs as well as the link between the folk medicine and drug development but also the necessity of natural products research. Some of the areas in which strategies for the conduct of natural product chemistry have changed include plant selection and collection, isolation techniques, structure elucidation, biological evaluation, semisynthesis and biosynthesis.

Strategies for research in the, area of natural products have evolved significantly over the last few decades. These can be divided into two categories:



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- A. Older strategies
- a) Focus on chemistry of compounds from natural sources, but not on activity.
- b) Straightforward isolation and identification of compounds from natural sources followed by biological activity testing.
- c) Chemotaxonomic investigation.
- d) Selection of organisms based on ethno pharmacological information or traditional uses.
- *B.* Modern strategies
- 1) Bioassay-guided isolation and identification of "lead" compounds from natural sources.
- 2) Production of natural products libraries.
- 3) Production of active compounds in cell or tissue culture, genetic manipulation, natural combinatorial chemistry.
- 4) More emphasis on bioactivity.
- 5) Introduction of the concepts of dereplication, chemical fingerprinting.
- *6)* Selection of organisms based on ethno pharmacological information, folkloric reputations and also those randomly selected. Natural products can contribute to the search for new drugs in three different ways:
- *a)* By acting as new drugs that can be used in an unmodified state (e.g., vincristine from *Catharanthus roseus*).
- *b)* By providing chemical "building blocks" used to synthesize more complex molecules (e.g., diosgenin from *Dioscorea floribunda* for the synthesis of oral contraceptives).
- *c)* By indicating new modes of pharmacological action that allows complete synthesis of novel analogs (e.g., synthetic analogs of penicillin from *Penicillium notatum*).

XIV. NATURAL PRODUCTS IN PHARMACEUTICALS

Natural products chemistry has become a mainstay in the pharmaceutical industry, along with the previous compounds, natural products research has brought about many new and successful treatments into all fields of medicine. Nowadays pharmaceutical research is tightly regulated and controlled allowing for a safer production of drugs and medications, plants are an excellent source of pharmaceutically active ingredients.

Active ingredients in plants are often found in:

- A. Bark, leaves and herbaceous portions of a plant.
- B. Seeds, blossoms and fruit.
- C. Root

Natural products and their derivatives have been invaluable as a source of therapeutic agents will undoubtedly provide a sound platform for the delivery of natural-product based therapeutic agent. Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value. The R&D thrust in the pharmaceutical sector is focused on innovative processes for known drugs and development of plant-based drugs through investigation of leads from the traditional systems of medicine [29].

Natural products also have a strong impact on human culture and have been used as condiments, pigments and pharmaceuticals in throughout human history. Pharmaceutical companies extract active ingredients from plants and sell them as drugs; the benefits of medicinal plants cannot be replicated because their synergistic combination of hundreds of naturally occurring phytochemicals cannot be reproduced in laboratories.

Many pharmaceuticals are consumed in unregulated markets for benefits in health concern and improvement of quality of life. Natural pharmaceuticals, nutraceuticals and cosmeceuticals are of great importance of chemical diversity aimed at new drug discovery and are explored for antimicrobial, cardiovascular, immunosuppressive and anticancer drugs. Their sales exceeded 65 billion in 2003.

Examples of plant products and derivatives used by the pharmaceutical industry include paclitaxel, vincristine, vinblastine, artemisinin, camptothecin, podophyllotoxin etc. There have been efforts to monitor, improve quality and regulate the growing business of herbal drugs. As the previous examples shown, natural products are important pharmaceuticals. In a study of the pharmaceuticals on the market from 1981-2002, only 43% of the drugs were purely synthetic, while the remaining 57% were derived from a natural source [30].

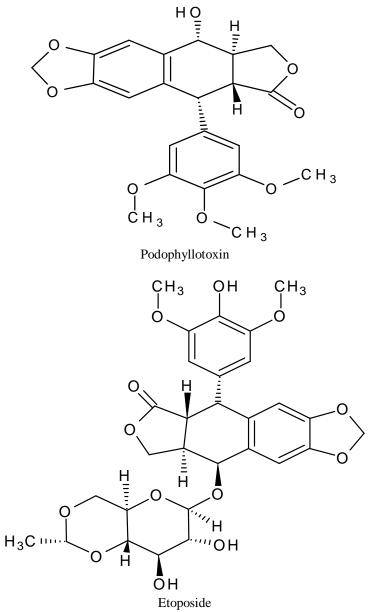


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XV. PLANT BASED ANTICANCER DRUGS

Biodiversity of the plant kingdom has provided a source of new drug for almost all disease areas. A variety of secondary metabolites obtained from natural origin showed good anticancer activity. Cancer is the second leading cause of death among children and it is responsible for 25% of all deaths [31]. Natural product based anticancer drug discovery is active area of research throughout the world. While cancer frequencies may vary from country to country, which include breast, colon, prostate, uterus, stomach, pancreas, liver, lung, urinary bladder, kidney, ovary, oral cavity and blood.

The object of research in cancer drug development is to find new drugs that are specific to cancer cells or develop a method that alters the nature of the drug administered such that it acts only on the target cells, thereby reducing the side effects. ⁵⁶One of the early compounds isolated as an anticancer agent was podophyllotoxin a compound obtained from *Podophyllum peltatum* in 1944 [32].



The Applied States

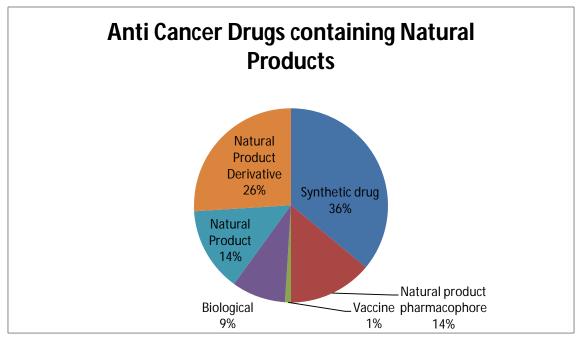


Fig: The role of natural products in anticancer drugs [30]

XVI. PLANT BASED ANTI HIV AGENTS

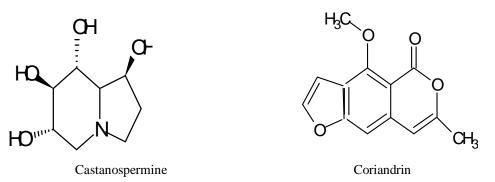
Most of the currently useful anti-HIV agents are nucleosides and emerging drug resistance. Natural products, with their broad chemical structural diversity, provide an excellent opportunity to deliver significant therapeutic advances in the treatment of HIV.

Acquired immune deficiency syndrome is a clinical syndrome that is the result of infection with human immunodeficiency virus (HIV), which causes immuno-suppression. It has been life-threatening health problem. The first case was identified in 1981 and is the most quickly spreading disease of the century. Since the epidemic spread, more than 60 million people have been infected with the virus [33].

Many natural products with novel structures have been identified as having anti-HIV activities. Betulinic acid isolated from Syzigium claviflorum, has been found to contain anti-HIV activity in lymphocytes. The quassinoside glycoside isolated from Allanthus altissima has been found to inhibit HIV replication [34]. Artemisinin, is of special interest because of its novel structure and activity against Pneumocystis carinii.

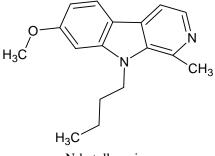
Most of the natural product chemicals that are attracting interest in this area of research are terpenes, phenolics, peptides, alkaloids, and carbohydrates and are also inhibitors of HIV reverse transcriptase. Calanolide A, isolated from Callophyllum lanigerum and two other natural product-derived molecules, bevirimat (DSB, PA-457) which is a 2, 2-dimethyl succinic acid derivative of betulinic acid and 3-hydroxymethyl-4-methyl DCK are phase II clinical candidates, as drugs for treatment of HIV infection [35] [36].

Castanospermine isolated from Castanospermum australe showed inhibition of HIV replication and syncytium formation induced by the envelope glycoprotein of HIV. It has also been reported to have glycosidase inhibitory activity [37]. Coriandrin isolated from the coriander Coriandrum sativum, possessed anti-HIV and other anti-viral activities[38].



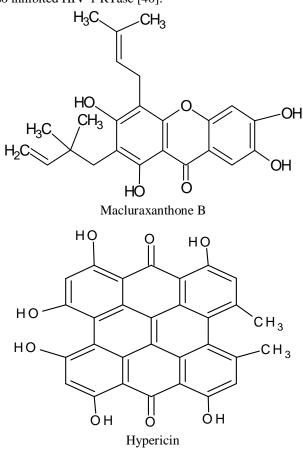


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N-butylharmine

Macluraxanthone B isolated from Maclura tinctoria exhibited moderate anti-HIV activity and hinokiflavone isolated from methanolic extracts of twigs and leaves of Rhus succedanea showed strong inhibition of the polymerase of HIV-1 RTase in in vitro assay [39]. Hypericin obtained from Hypericum perforatum showed activity against non-human retrovirusesas well as human retroviruses in lymphocytes. It has also inhibited HIV-1 RTase [40].



XVII. RESEARCH AREAS IN NATURAL PRODUCTS TODAY

- A. Structural elucidation (speed of analysis, sample throughput complexity of structures).
- B. Synergy and biotransformation.
- C. Biosynthesis.
- D. Biological activity.
 - 1) Ecological



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- 2) Pharmaceutical properties / drug discovery
- *3)* Healthcare and cosmetic products
- E. Molecular biology and Biotechnology
- F. Quantitative natural products chemistry

XVIII. CONCLUSION

Nature still holds many secrets which we can learn from; chemical structure, biosynthesis, the role and relationship of plants to other organisms. The study of natural products merges science with culture. For countries which harbor rich biodiversity, the study of natural products is an important way of developing one's natural resources. Natural products should use the new developments, e.g., molecular biology, computational science.

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