

Natural Products: Source of Potential Drugs

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Abstract: Natural products isolated from various sources especially derived from plants, have long been used in treatment of human ailments. For long time, the approach to new drugs through natural products was proved to be the single most successful strategy for the discovery of new drugs. Despite the initial success, chemical diversity and specific action on target, drug discovery from natural products, has been deemphasized by many pharmaceutical companies in favour of approaches based on combinatorial chemistry and genomics. Besides covering the historical notes and the drugs already isolated from different natural sources like plants, fungi, marine organisms and animals, this review article is also presenting the reasons for the leg back in the field. Natural products have a large unexplored range of compounds, which is almost impossible to imitate; they will always remain a potential source of future drug discovery.

Key words: Natural products • Chemical diversity • Drug discovery • Combinatorial chemistry • Genomics

INTRODUCTION

The term natural product refers to any naturally occurring substance, but, is generally taken to mean a secondary metabolite; small molecule that is not involved in the main life processes i.e. primary metabolism of the cell, like the growth and development, instead formed as peculiar off shoots along specific biogenetic pathways. It has been estimated that well over 300,000 secondary metabolites exist [1] and it's thought that their primary function is to increase the likelihood of an organism's survival by repelling or attracting other organisms.

Prior to the 1800s, the active constituents of most medicines, which were generally plant-based and mostly used as extract, decoction, oil, powder, mixture etc. were unknown. With the increase in science based knowledge, advancement in separation, isolation and characterization techniques, made it possible to isolate and identify active chemical compounds found in crude extract or paste of natural products' resource in use.

Natural Products as Therapeutic Agents: History: As Rudyard Kipling wrote (1910), "Anything green that grew out of the mould was an excellent herb to our fathers of old. 'Since the dawn of medicine, compounds derived

from plants have been used as therapeutic agents date back thousands of years [1]. The oldest records date back to 2600 B.C. were written on clay tablets and come from Cuneiform in Mesopotamia [2]. These records indicate that there were many, up to 1000 plant based 'drugs' used in that time. Many of these agents are still used as treatments for inflammation, influenza, coughing and parasitic infestation [3]. Egyptians have been found to have documented uses of various herbs in 1500 B.C. [4]. The best known of these documents is the "*Ebers Papyrus*", which documents nearly 1000 different substances and formulations, most of which are plant-based medicines [5].

Repeatedly documented, The Chinese "*Materia Medica*" [6] (1100 B.C.) (Wu Shi Er Bing Fang, contains 52 prescriptions), "*Shennong Herbal*" (~100 B.C., 365 drugs) and the "*Tang Herbal*" (659 A.D., 850 drugs) contain the records of the uses of natural products [7].

A collection of Ayurvedic hymns in India from 1000 B.C. describes the uses of over 1000 different herbs [8]. "Ayurveda" is derived from the Indian words Ayar (Life) and veda (Knowledge or Science) and hence means the Science of Life. Following the system would help ensure a long life, which is considered to be the instrument for achieving righteousness (dharma), wealth (artha) and

happiness (sukha) [8]. This work served as the basis for Tibetan Medicine translated from Sanskrit during the eighth century [6].

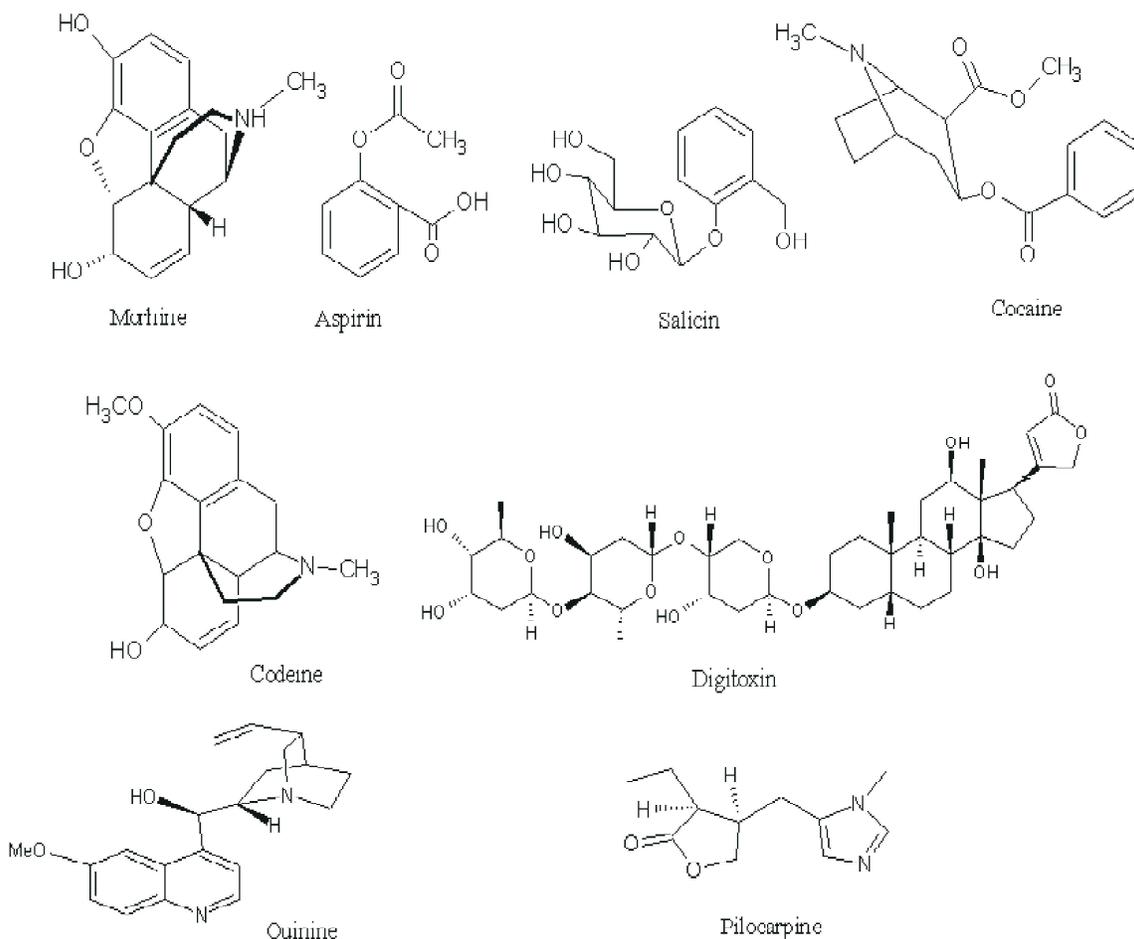
The Greek philosopher and natural scientist, Theophrastus (~300 B.C.) wrote "*History of Plants*" in which he addressed the medicinal qualities of herbs and the ability to cultivate them [9]. The Greek physician, Pedanious Dioscorides (100 A.D.), produced a work entitled "*De Materia Medica*", which still today is a very well-known European document on the use of herbs in medicine [8]. Galen (130–200 A.D.), practiced and taught pharmacy and medicine in Rome and published over two dozen books on his areas of interest [8]. He was well-known for his complex formulations containing numerous and multiple ingredients [9].

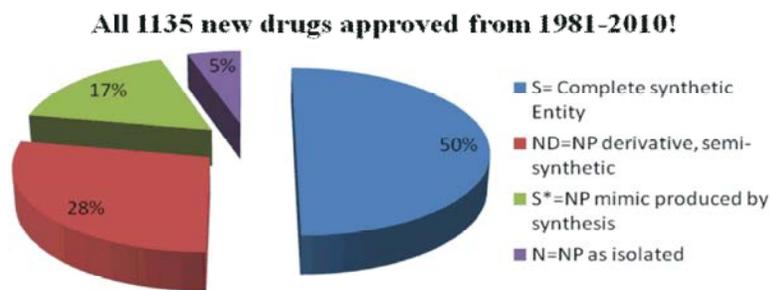
Monks in monasteries in the Middle Ages (500-1200 A.D.) copied manuscripts about herbs and their uses [10]. The Persian philosopher and physician Avicenna produced a work entitled "*Canon Medicinae*", which is considered to be the definitive summarization of

Greek and Roman medicine [8]. Li Shih-Chen produced a Chinese drug encyclopedia during the Ming Dynasty entitled "*Pen-ts'askang mu*" in 1596 A.D., which records 1898 herbal drugs and 8160 prescriptions [5]. The most complete reference to Chinese herbal prescription is the Modern Day Encyclopedia of Chinese materia medica published in 1977. It lists nearly 6000 drugs out of which 4800 are of plant origin [8].

Drug Discovery from Natural Products: In 1803/04, Friedrich Wilhelm Sertürner succeeded in isolating a crystalline substance from opium in the test tube, which he named morphine [11]; a commercially important drug later marketed by E. Merck in 1826 [12].

The first semi-synthetic pure drug aspirin, based on a natural product salicin isolated from *Salix alba*, was introduced by Bayer in 1899. This success subsequently led to the isolation of early drugs such as cocaine, codeine, digitoxin, quinine and pilocarpine, of which some are still in use [4, 12, 13].





Source: Newman and Clark, J. Nat. Prod. 2012, 311.

Fig. 1: Contribution of natural products in total drugs discovered in three decades

The introduction of the sulphonamide antibiotics in the 1930s and penicillin in the 1940s revolutionised natural products based drug discovery process and considerably decreased the fatality rates associated with bacterial infections [13]. More than 80% of drug substances involved in drug discovery programs in “olden times” (i.e. before the advent of high-throughput screening (HTS) and the post-genomic era) were reported to be natural products or inspired by natural product structures [3,14,15]. It is arguably still true; comparisons of the information presented on sources of new drugs from 1981 to 2007 indicate that almost half of the drugs approved since 1994 are based on natural products [4, 16, 17].

Natural products have been the biggest single source of anti-cancer drugs [17]. Of the 175 anti-cancer agents developed and approved over the seven decades from 1940 until 2010 in Western countries and Japan, 85 compounds representing 48.6%, were natural products or directly derived from natural products [18].

According to a recent research published 38 natural product-derived drugs were approved in the decade from 2000 to 2010 for various indications including 15 for infectious diseases, 7 each for oncology, neurological diseases and cardiovascular disorders, 4 for metabolic disorders and 1 for diabetes [4]. It has been reported that 49 plant-derived, 54 microorganism derived, 14 marine organism derived (including 2 from fish and 1 from a cone snail) and 1 terrestrial animal derived (bovine neutrophils) drug candidate(s) are in various phases of clinical evaluation [4].

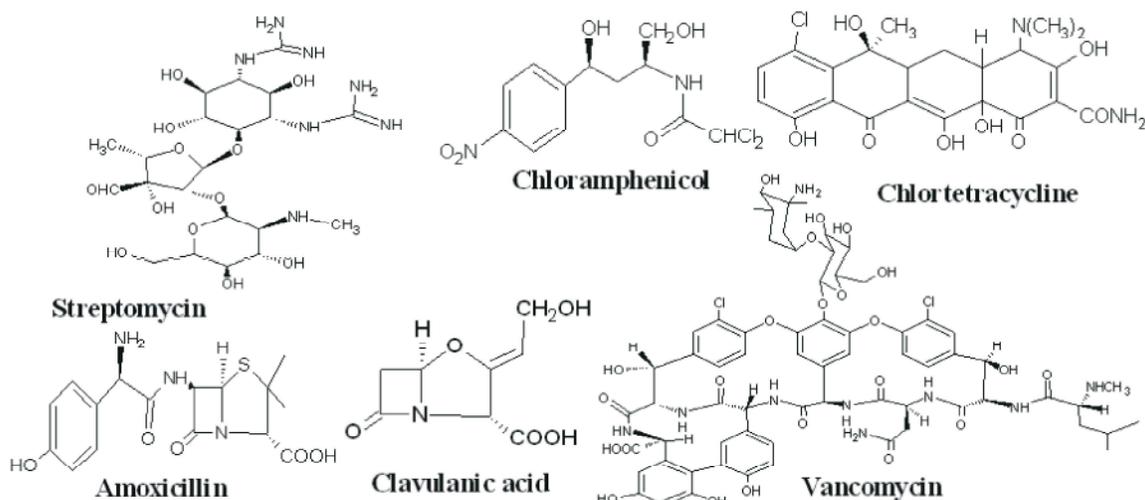
Drugs Derived from Fungi: The fungal kingdom contains some of the most important organisms, in terms of their economic and ecological roles and includes many well known fungi such as mushrooms, rusts, smuts, puffballs, truffles, morels, moulds and yeasts. Fungi are known to cause a number of plant and

animal diseases but the study of fungal metabolites have provided many compounds that are proved as antibiotics, antifungal, immunosuppressive and cholesterol lowering agents.

The discovery of penicillin from *Penicillium notatum* by Fleming in 1928, re-isolation and clinical studies by Chain, Florey and co-workers in the early 1940s and commercialisation of synthetic penicillins revolutionised drug discovery research [19]. The huge success of penicillin prompted a worldwide effort by drug companies and research groups to assemble large collections of microorganisms in order to try and discover new antibiotics [20]. The effort paid off and in fact the early years were extremely prolific and included the discovery of streptomycin, chloramphenicol, chlortetracycline, cephalosporin C, erythromycin and vancomycin. All of these compounds or derivatives thereof are still in use as drugs to this day [19, 21]. In the early 1970s β -lactamase inhibitor, clavulanic acid, from *Streptomyces clavuligerus* has been isolated [22]; mixture of clavulanic acid and amoxicillin, known as augmentin is still in use today as a front-line antibiotic.

Success stories include, the cholesterol-lowering agent, mevinolin [23], one of the so-called statins, isolated from *Aspergillus terreus* and asperlicin [24], a cholecystokinin (CCK) antagonist from *Aspergillus alliaceus*. Structure manipulation of this compound has led to the discovery of the benzodiazepines [25] used for the treatment of severe anxiety or insomnia.

Most of the fungi live in the intercellular spaces of plant stems, petioles, roots and leaves without affecting the host organism and are called endophytes. The endophytic fungus, *Cytospora sp.* has yielded two human cytomegalovirus (hCMV) protease inhibitors, cytonic acids A and B [26]. hCMV is a ubiquitous opportunistic pathogen that causes disease in those that are congenitally immunodeficient.



Endophytic fungus *Cryptosporiopsis quercina* isolated from *Tripterigeum wilfordii* (a medicinal plant native to Eurasia) has shown antifungal activity against some important human fungal pathogens, including *Candida albicans* and *Trycophyton mentagrophyte* [27]. A novel peptide cryptocandin is proved as the bioactive principle and is currently being considered for use, against fungal diseases of the skin and nails [27].

Aspergillus parasiticus, an endophyte of the coastal redwood (*Sequoia sempervirens*), was found to produce the sequoiatones A and B. These compounds showed moderate and selective inhibition of human tumour cells, with the greatest activity against breast cancer cell lines [28, 29].

An investigation of an unidentified endophytic fungus from Costa Rica for antibiotic activity yielded guanacastepene A [30]. It was shown to display antibiotic activity against methicillin-sensitive and -resistant *Staphylococcus aureus* (MSSA and MRSA) and vancomycin resistant *Enterococcus faecalis* (VRE) [30]. It has been suggested that the primary mode of bactericidal action is membrane damage.

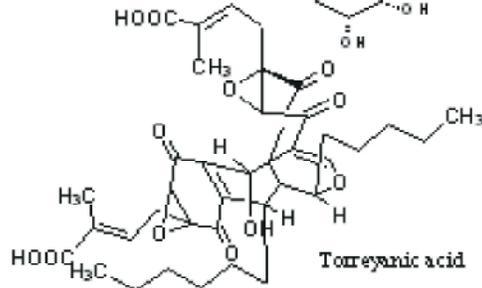
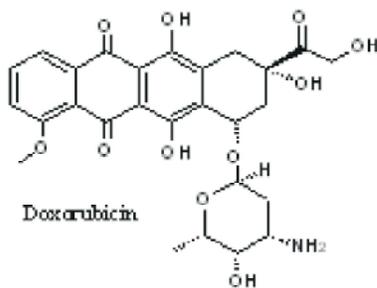
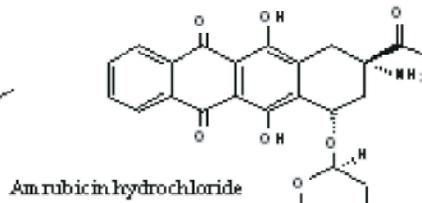
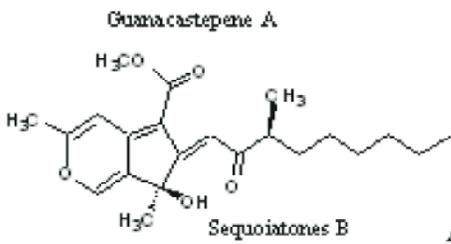
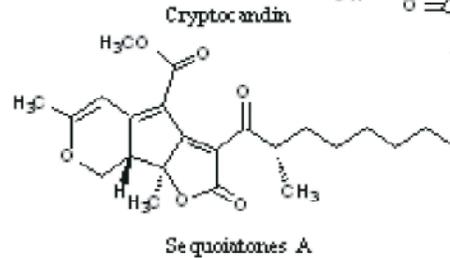
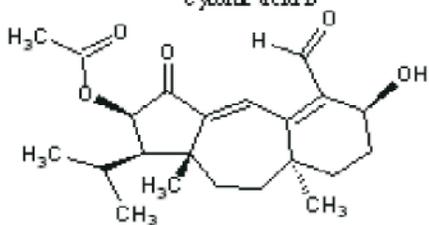
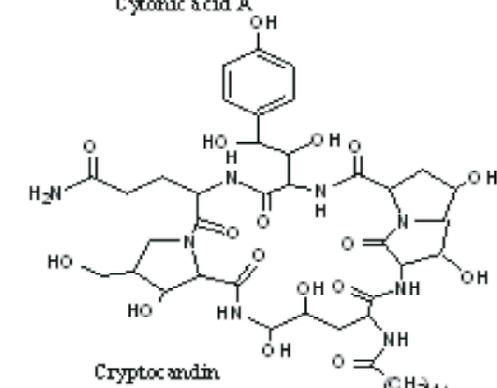
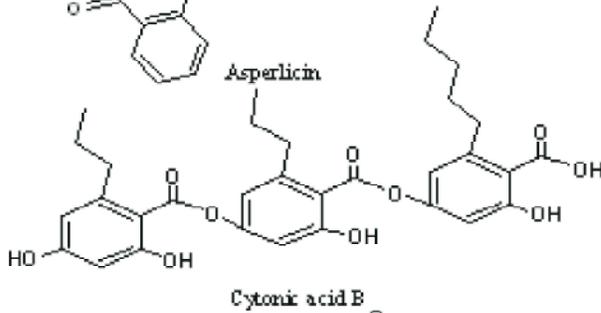
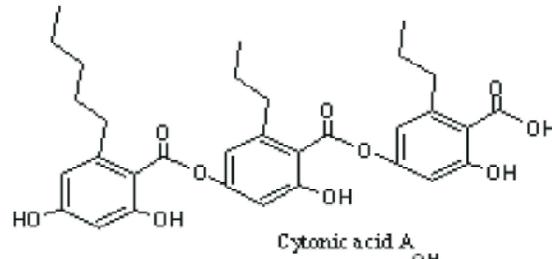
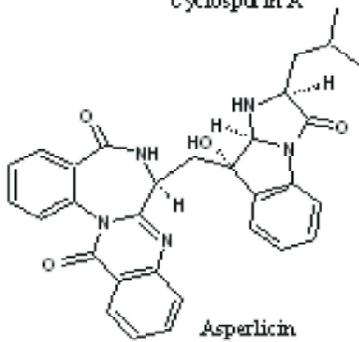
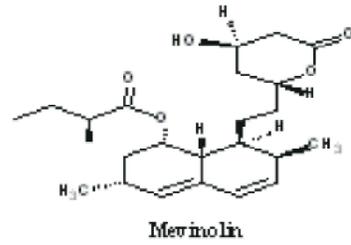
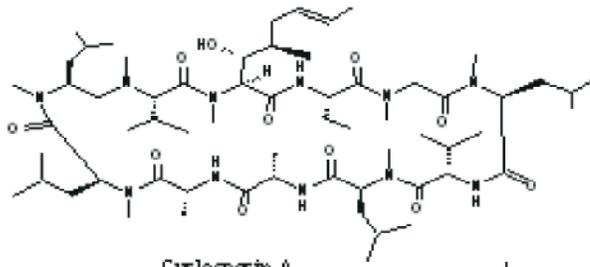
In 2002, Amrubicin hydrochloride, related to the anthracycline, doxorubicin (Adriamycin®), was isolated from the fungus *Streptomyces peucetius* [31]. Doxorubicin is used to treat acute leukaemia, soft tissue and bone sarcomas, lung cancer, thyroid cancer and both hodgkins and non-hodgkins lymphomas [32].

Torreyanic acid was isolated from an endophyte from the endangered tree, *Torreya taxifolia* and was tested in several cancer cell lines and found to display 5–10 times greater cytotoxicity in cell lines that are sensitive to protein kinase C causing cell death by apoptosis [31].

Drugs Derived from Plants: Natural Products act as lead molecules for the synthesis of various potent drugs. The plant-derived compounds have a long history of clinical use, better patient tolerance and acceptance. A significant number of drugs have been derived from plants that were traditionally employed in ethnomedicine or ethnobotany, while others were discovered initially through random screening of plant extracts in animals or later, by determining their biological activity either *in vitro* or *in vivo* [33].

In the early 1900's, 80% of all medicines were obtained from roots, rks and leaves and approximate estimation is that, 25% of all drugs prescribed today still originate from plants [34, 35]. The plant kingdom, with 300,000 to 400,000 higher species is always a key source of new chemical entities (NCEs) for active pharmaceutical ingredients and lead compounds [36]. It is estimated that only 5% to 15% of these terrestrial plants have been chemically and pharmacologically investigated in a systemic fashion [34]. Approximately 10,000 to 15,000 of the world's plants have documented medicinal uses and roughly 150-200 have been incorporated in western medicine [34, 37, 38]. According to a report by BCC Research, the global plant-derived drug market was valued at US\$ 22.1 billion in 2012 and sales are projected to grow to US\$ 26.6 billion by 2017 at a compound annual growth rate (CAGR) of 3.8% [33,38].

Anti-Cancer Drugs from Plants: Cancer is a global epidemic, WHO fact sheet about cancer accounts worldwide approximately 7.6 million deaths (around 13 % of all deaths) in 2008. Cancer incidences are continuously on the rise, according to cancer progress report, 2013 by American Association for Cancer Research (AACR), 13 million people may die with this fatal disease by 2030.



The four major structural classes of plant derived cancer treatments include vinca alkaloids, epipodophyllotoxin lignans, taxane diterpenoids and camptotectin quinolone alkaloid derivatives. Approximately 30 plant derived anti-cancer compounds have been reported to be clinically active against various types of tumors and are currently used in clinical trials [39]. The history of natural products as anticancer agents has been started with discovery of podophyllotoxin from the podophyllum peltatum in 1947 [40]. Podophyllotoxin acts by preventing the polymerization of tubulin into microtubules. Two derivatives of podophyllotoxin named etoposide and teniposide are in the market [41]. These compounds arrest cell growth by inhibiting DNA topoisomerase II, preventing the cleavage and resealing of DNA strands [42].

The 'vinca alkaloids', vinblastine and vincristine are discovered from the Madagascan periwinkle, *Catharanthus roseus* and are used in the effective treatment of Hodgkin's disease and childhood leukemia, respectively [13]. Both are antimetabolic drugs and like podophyllotoxin by binding tubulin, prevent polymerization of these into microtubules [42].

In 1966 a cytotoxic quinoline alkaloid camptothecin (CPT), was isolated by M. E. Wall and M. C. Wani from the bark and stem of a tree native in China i.e. *Camptotheca acuminata*. Mechanism wise it is a topoisomerase inhibitor drug type but has low solubility and high adverse drug reactions. That's why two CPT analogues topotecan and Irinotecan have been developed and are being used in cancer chemotherapy now a day's [43].

In the search of more anti-cancer drugs the Pacific yew tree, *Taxus brevifolia*, was investigated and paclitaxel (Taxol®) was discovered as its active principle [44]. This compound has a unique cytotoxic mechanism; this is the first anticancer drug discovered that stabilizes microtubules and thus promotes their polymerization. Since its discovery, it has become a blockbuster drug used in the treatment of lung, ovarian and breast cancer and Kaposi's sarcoma [45].

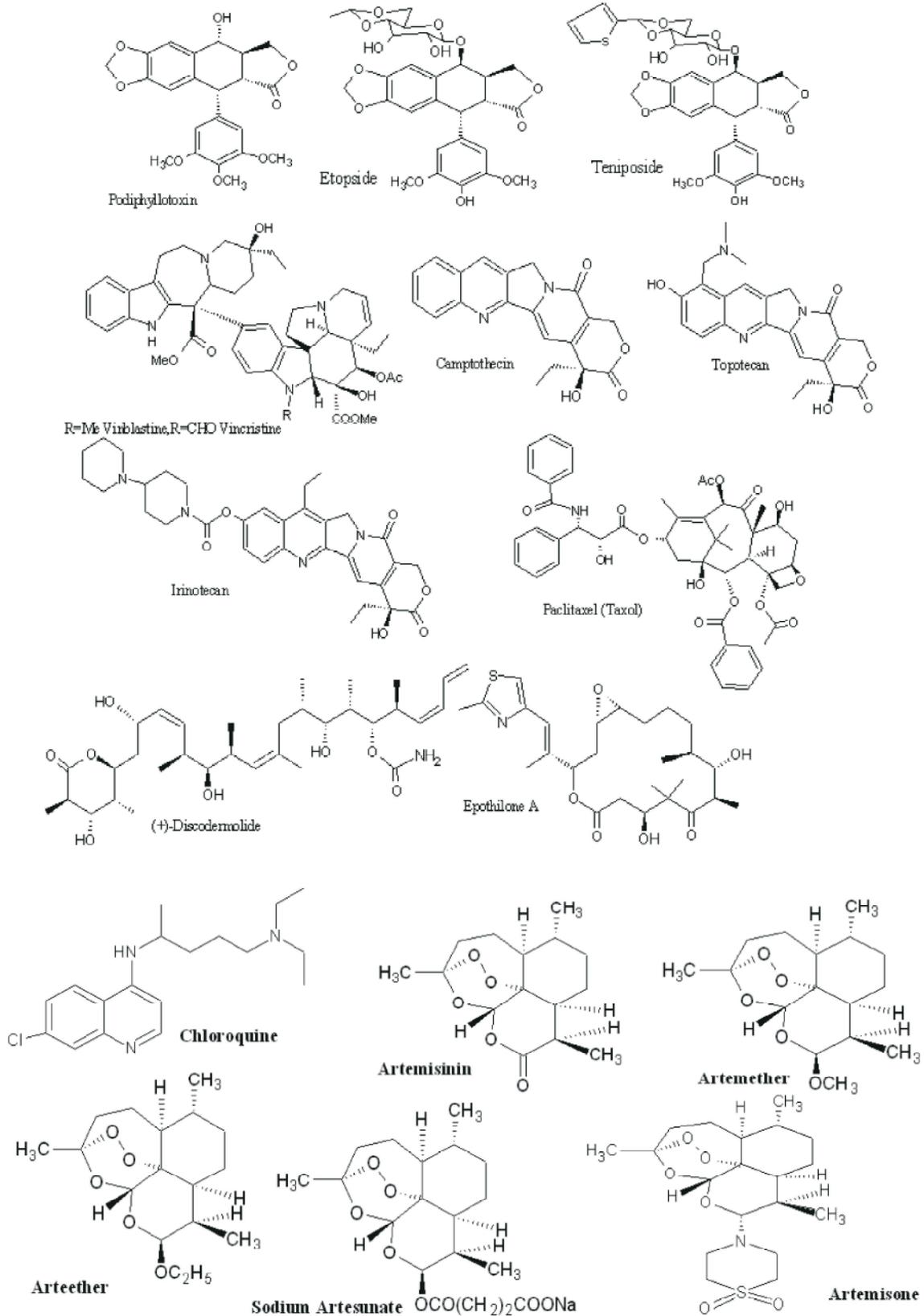
On the basis of drug mechanism of paclitaxel other compounds like (+)-discodermolide and the epothilones such as epothilone A have also been discovered [46, 47] that act in same manner and even show activity against multidrug-resistant cell lines. It has even been observed that paclitaxel and discodermolide have a synergistic effect when administered together [48].

Antimalarial Drugs from Plants: Malaria is by far the most important tropical disease with 300 to 500 million clinical cases and about 2 million deaths of mainly infants and young children every year [49]. Quinine extracted from *Cinchona officinalis* bark, was the first and only antimalarial drug for a long time [50]. Intense efforts were made during the World War II to find more accessible anti-malarial agents and resulted in the development of chloroquine as a very potent drug. However, the emergence of chloroquine resistant *Plasmodium falciparum* strains led to a steady deterioration of the situation with the increase malaria mortality rate [50].

The discovery of artemisinin in 1972 from the leaves of traditional Chinese plant *Artemisia annuata*, which has been used for over 2000 years by the Chinese to treat malaria [51], was the starting point of one of the most remarkable advances in the chemotherapy of malaria. Artemisinin is a sesquiterpene lactone with a highly unusual endoperoxide group in a 1,2,4 trioxane ring that is crucial for the activity. This compound is highly effective, even in the cases incurable by chloroquine but its high lipophilicity led to problems with its administration as a drug [50]. In attempts to prepare semi-synthetic derivatives of artemisinin by scientists, some most active compounds like artemether, artesunate and sodium artesunate have come into existence [50].

Attempts have been made to develop new derivatives with improved properties, in particular by synthesizing C-10 carbon-substituted analogs. A representative compound, artemisone is currently evaluated in Phase I clinical trials by Bayer AG and Medicines for Malaria Venture (MMV) [51].

Antiviral Drugs from Plants: Acquired immunodeficiency syndrome (AIDS) is a devastating disease caused by the human immunodeficiency virus (HIV) and has led to more than 25 million deaths worldwide since the first cases were reported in 1981 [48]. Four classes of drugs are currently in use: nucleoside analog reverse transcriptase inhibitors [52], protease inhibitors, non-nucleoside reverse transcriptase inhibitors [53] and one fusion inhibitor [54]. A major breakthrough in AIDS therapy was the introduction, in the late 1990s, of drug combinations from two or more classes of inhibitors, a strategy termed highly active antiretroviral therapy (HAART) [48].



In one of the largest screening programs by the NCI (National cancer Institute), USA between 1987 -1996 over 30,000 plant extracts were tested for in vitro cell-based anti-HIV assay [55]. These screening efforts resulted in the discovery of a considerable number of compounds exhibiting in vitro anti-HIV activity. While there is still no anti-HIV drug of plant origin in the market, several plant metabolites proved to be valuable lead compounds. Some of these compounds or derivatives have advanced to clinical or preclinical development [48].

In 1987 an antiviral compound coumarin calanolide A was isolated from an extract of leaves and twigs of the tree *Calophyllum lanigerum* (Clusiaceae) collected in Sarawak, Malaysia [56]. At the same time, a diastereomer, calanolide B was also isolated from the latex of related species *C. teysmanii*. The calanolides were licensed by the NCI to Medichem Research Inc and are now being developed by Sarawak medichem pharmaceuticals, a joint venture company between the Sarawak state government and Medichem Research Inc [57].

Calanolides act as non nucleoside reverse transcriptase inhibitors. The clinical development of calanolide A started in 1997. The compound is now obtained by synthesis and is currently in Phase II trials, while calanolide B is in preclinical development [58]. These two compounds are also found to be active against *Mycobacterium tuberculosis* [59].

Another success story by NCI, was the isolation of phorbol ester prostratin in 1992 from the wood of *Homalanthus nutans* (Euphorbiaceae), a tree used by traditional healers in Western Samoa for the treatment of viral hepatitis [60]. The further development of prostratin is conducted by the AIDS Research Alliance in Los Angeles, California (ALA). In 2010, Phase I human clinical trials of prostratin were also carried out [31] and if prove to be safe, in the future it could become a highly promising clinical candidate for adjunctive use in AIDS therapy.

Besides above mentioned compounds synthetic derivatives of some other natural products e.g. pyranocoumarin suksdorfins isolated from fruit of *Lomatium suksdorfii* (apiaceae) [61], lupane triterpene betulonic acid isolated from Taiwanese herb *Syzygium claviflorum* (myrtaceae) [62] etc. are also being prepared in different parts of world by scientist and are under different stages of pre-clinical and clinical trials to get a universally accepted and promising anti HIV drug.

Miscellaneous: Grandisines A and B are two indole alkaloids which were isolated from the leaves of the Australian rainforest tree, *Elaeocarpus grandis*. Both the compounds exhibit binding affinity for the human δ -opioid receptor and are potential leads for analgesic agents [63].

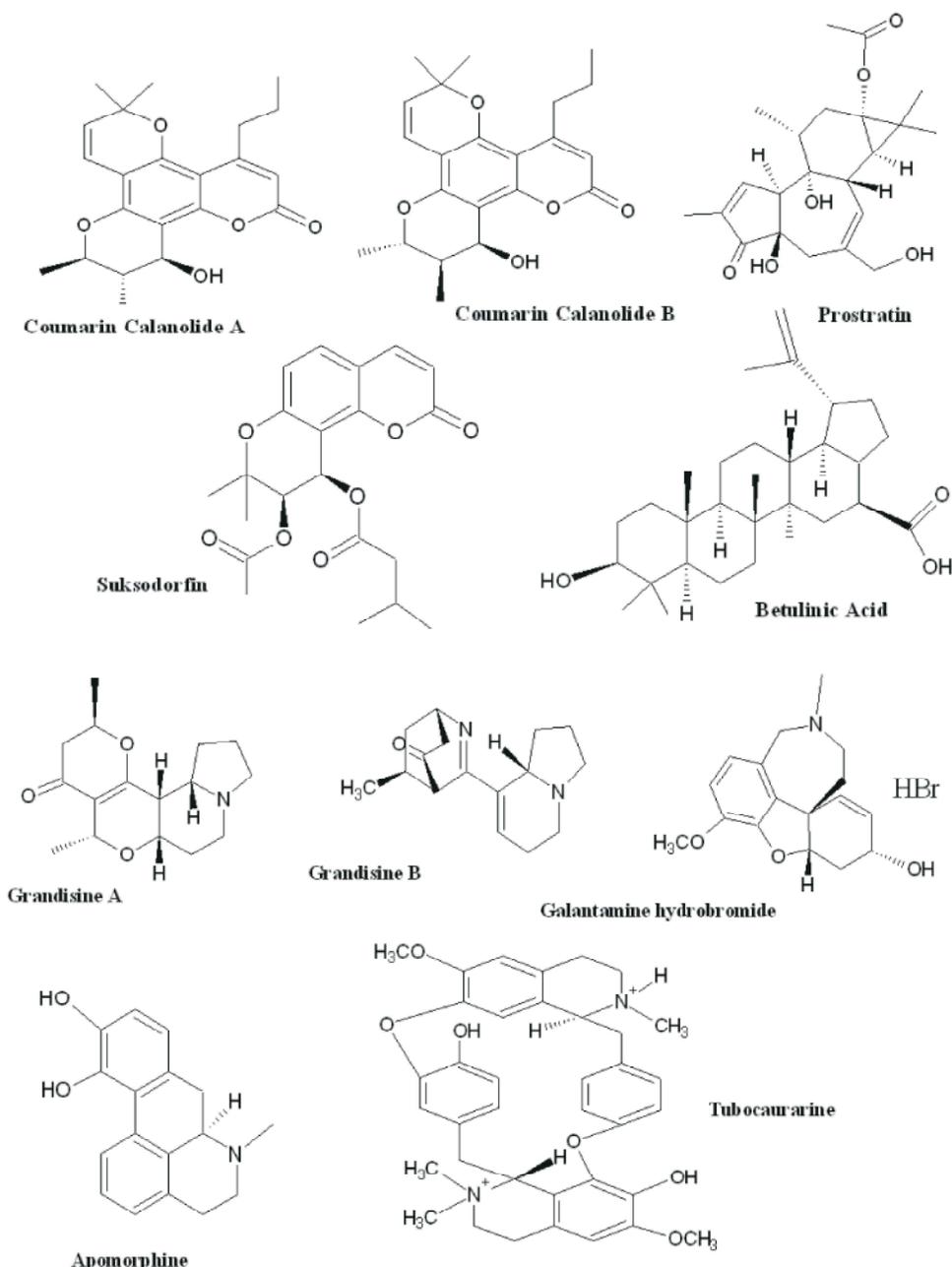
Galantamine hydrobromide is an example of ethnobotany-driven drug discovery. It is an alkaloid obtained from a plant *Galanthus nivalis* (Amaryllidaceae) that is traditionally used as a powerful medicine in Turkey and Bulgaria for neurological disorders. In USA it is FDA approved drug for the treatment of alzheimer's disease [64].

Apomorphine is a derivative of morphine isolated from the poppy (*P. somniferum*) and is a short-acting dopamine D1 and D2 receptor agonist, as well as a potent dopamine agonist, used to treat parkinson's disease [65].

“Curare” is the arrow poison of the South American Indians and is prepared in the rain forests of the Amazon and Orinoco [31]. Tubocaurarine isolated from the climbing plant, *Chondrodendron tomentosum* (menispermaceae) is one of the active constituents used as a muscle relaxant in surgical operations, reducing the need for deep anesthesia [31].

Drugs Derived from Marine Organisms: About 70% of the earth's surface is covered by the oceans, providing significant biodiversity for exploration for drug sources. Many marine organisms have a sedentary lifestyle, for survival they synthesize many complex and extremely potent chemicals as means of defence from predators [66]. Natural products released by marine organisms directly come into the water, so get rapidly diluted, they must be very potent materials to have the desired end effect. These chemicals can serve as possible remedies for various ailments, especially cancer [66].

The interest in novel chemical structures from marine organisms started in the 1950s as marine animal taxonomy advanced significantly, but progressed at a slow pace for the first two decades before it started to burgeon in the 1970s [67, 68]. Since then, approximately 30,000 structurally diverse natural products with a vast array of bioactivities have been discovered from marine organisms including microbes, algae and invertebrates [67, 69]. Marine invertebrates alone were described as the source of almost 10,000 new natural products since 1990 with a



pronounced increase to about 1,000 compounds per year in more recent years [70]. The global marine pharmaceutical pipeline consists of 3 Food and Drug Administration (FDA) approved drugs, 1 EU (European Union) registered drug, 13 natural products (or derivatives thereof) in different phases of the clinical pipeline and a large number of marine chemicals in the pre-clinical pipeline [31, 71].

The first notable discovery of biologically active compounds from marine sources can be considered the isolation and identification of C-nucleosides,

spongouridine and spongothymidine from the caribbean sponge, *Cryptotheca crypta* in the early 1950s [72]. These compounds are nucleotides and show great potential as anticancer and antiviral agents. The synthesis of structural analogues led to the development of cytosine arabinoside (Ara-C) as a clinical anticancer agent, together with (Ara-A) as an antiviral agent 15 years later [31, 72].

Plitidepsin (Aplidin®, PharmaMa), a depsipeptide was isolated from the mediterranean tunicate *Aplidium albicans*. Plitidepsin is effective in treating

various cancers, including melanoma, small cell and non-small cell lung, bladder as well as non-hodgkin lymphoma and acute lymphoblastic leukemia [71, 73] and is currently in phase III clinical trials [74].

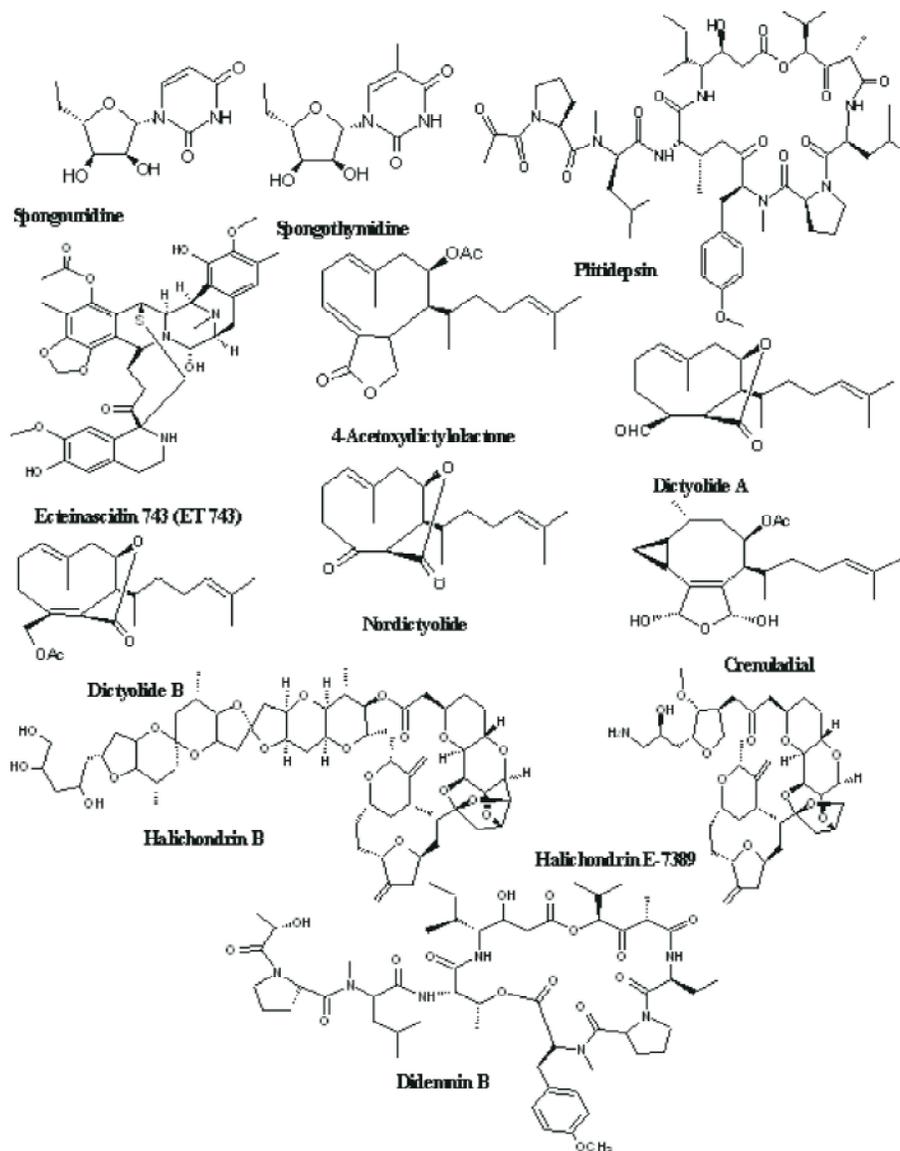
In 2007 trabectedin also known as ecteinascidin 743 (ET743; Yondelis™) became the first marine anticancer drug to be approved in the European Union [71]. It has been isolated from the ascidian *Ecteinascidia turbinata* [75].

Diterpenes, 4-acetyoxydictyolactone, dictyolides A, B and nordictyolide isolated from the brown alga, *Dictyota dichotoma* display antitumor activities [76], while crenuladial, obtained from the brown alga

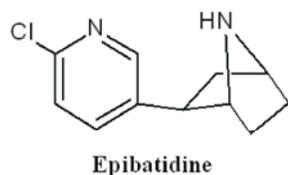
Dilophus ligatus has shown antimicrobial activity against *Staphylococcus aureus*, *Micrococcus luteus* and *Aeromonas hydrophyla* [77].

Halichondrin B is isolated from *Halichondria okadae* (Japan) [78] and other sponges. The structural analogue of this compound halichondrin E-7389 has been selected for further development and is currently in phase III clinical trials for the treatment of breast carcinoma [79]

Didemmins are cyclic depsipeptide compounds isolated from a tunicate of the genus *Trididemnum* in 1978 [80]. Out of 9 isolated compounds, didemnin B is found most biologically active and currently under clinical trial phase –II as an anticancer agent [80].



Drugs Derived from Animals: Animals have also been a source of some interesting compounds that can be used as drugs. Epibatidine, obtained from the skin of an ecuadorian poison frog, is ten times more potent than morphine [81]. Venoms and toxins from animals have played a significant role in designing a multitude of cures for several diseases.



Epibatidine

Drug Discovery Process: Drug discovery from natural product is very long, tedious process and involves two approaches, first one is chemically driven (finding biological activities for purified compounds) and second is biologically driven (bioassay guided approach beginning with crude extracts) or it can be combination of the both. The majority of the academic based research efforts have now become essentially ‘biologically driven’ i.e., the object of the research has shifted to discover natural products with biological activity. The chemically driven process can be divided in following steps:

- Identification of natural material.
- Preliminary screening of the crude extract.
- Isolation of various secondary metabolites.
- Elucidation of their structures with the use of advanced HPLC, high resolution 2D-NMR and other spectroscopic methods.
- Evaluation of biological activity (*in vitro* and *in vivo*) of every isolated individual molecule.
- Preclinical studies such as toxicity, stability and solubility studies, pharmacokinetic and mechanism studies to predict the plausible mode of action, for the pharmacologically active isolated molecules.
- Development of process for economical and easy isolation of those molecules from their sources, which are found more active than existing drugs
- The last ordeal is clinical trials where the candidate molecule is tested for its safety and efficacy on several group of human volunteers.

Counting pre-clinical and clinical trials time, it takes almost a decade for new candidate drug to get approval for launch in market. In most of the cases natural product as a drug are limited to the active extract (containing

mixture of compounds) like most of the ayurvedic herbal formulations due to their poor bioavailability and high input costs.

In other direction, molecules which are of limited use to be developed as an individual drug are subjected to chemical modifications or partial derivatization to increase their therapeutic use. In case of poor bioavailability feasible synthetic schemes can also be developed to produce lead active molecule.

Natural Products Based Drug Discovery: Challenges:

Of the 1355 small-molecule New Chemical Entities (NCEs) introduced between 1981-2010, only 387 (29%) are purely synthetic, otherwise all are natural products, semi-synthetic natural product analogues or synthetic compounds based on natural product pharmacophores [81]. Despite this success, the pharmaceutical industry, in particular the large pharmaceutical companies de-emphasized natural product discovery research in the 1990s and early 2000s. Several reasons have been blamed for the decline:

- Automated high throughput screening (HTS) programs increased the speed at which libraries of samples could be tested for bioactivity and most natural product programs could not meet the increased demand for the sheer numbers desired for successful HTS. That drifted many companies to move away from natural product extract libraries towards ‘screen friendly’ synthetic chemical libraries [82].
- Combinatorial chemistry was also being promoted as a better approach for creating large sets of “drug-like” chemical compounds with wide chemical diversity for supporting the HTS efforts [82].
- Advances in molecular biology, cellular biology and genomics increased the number of molecular targets and prompted shorter drug discovery timelines.
- A decline in the focus of major pharmaceutical companies on therapy for infectious diseases, which has been a traditional area of strength for natural products.
- Possible uncertainties regarding the collection of biological materials as a result of the 1992 Rio Convention on biological diversity [22], Seasonal or environmental variations in the composition of living organisms, Loss of source due to deforestation, environmental pollution as well as global warming.

- Generally the isolation of very small quantity of bioactive compound from the initial complex mixture of bio-genetic material. That is many times insufficient for detection by HTS, even in some cases the key compound is found unstable in the mixture.
- A further complication can be due to synergistic or antagonistic activity of two constituents that may then diminish or disappear upon separation.
- Screening of natural product sources is a tedious, lengthy process with a high

Probability of duplication that is the result may be a known compound that cannot be patented.

Natural Products: Future Perspective: Despite the challenges discussed before still natural products inherent enormous potentialities for new drug discoveries.

- Combining the strengths of the knowledge based on traditional systems such as ayurveda and other medicinal systems, with the dramatic power of combinatorial chemistry and HTS can help in the generation of structure–activity libraries. Traditional knowledge and experiences based database can provide new functional leads to reduce time, money and toxicity – the three main hurdles in drug development [83].
- The current ‘one drug fits all’ approach may be unsustainable in the future. In the management of polygenic syndromes and conditions, there is a renewed interest in multi-ingredient synergistic formulations. Rationally designed polyherbal formulation is being developed as option for multi-target therapeutic and prophylactic applications. This approach can offer economical alternatives, as it saves time and money required in isolating and characterizing individual compounds from complex mixture [84].
- “Dereplication” is the process of identifying known compounds that are responsible for the activity of an extract before bioassay-guided isolation has started. This process is used to eliminate or prioritize extracts for further study and can save considerable research time [21].
- With the development of advance isolation and characterization techniques like HPLC-MS and HPLC-NMR etc. the difficulty in isolating and characterizing complex natural products is becoming less of a problem. In addition, microprobe NMR will

lessen the sample size requirements for structure elucidation.

- Problems with resupply and large scale production can be minimized by careful collection work, using GPS to return to the exact location of the original collection. Large scale production can sometimes be carried out by semisynthesis (as in the case of taxol) or by total synthesis (as in the case of E7389) [85].
- Some combinatorial libraries though contain millions of synthetic compounds with significant chemical diversity but still are of no use for drug development. The libraries based on biologically-relevant chemical diversity or properties are much more useful than based on chemical accessibility and maximum achievable size.

According to Danishefsky: “A small collection of smart compounds may be more valuable than a much larger hodgepodge collection mindlessly assembled” [86].

“Biological friendliness” and “drug likeness” take natural products far ahead to be developed as drugs than synthetic compounds. The potential for undesired side effects due to the often less specific binding characteristics of many of the simple combinatorial generated molecules creates a renewed interest in natural products as a source of chemical diversity and lead compound generation.

- The ‘catalogue’ of natural products is still far from complete. Discoveries of new structures and functions are likely to continue as unexplored sources of natural products are evaluated. The functional group diversity and design introduced into natural products during biosynthesis continues to provide lessons for chemists in how to construct biologically active mimics and provide selective ligands for cellular targets.

CONCLUSION

Though discovery of drugs from natural products is a long, tedious process and is associated with unpredictable results, but still with technical advancements, it’s possible to screen and evaluate the pharmacological activities of constituents present in natural resources efficiently. In fact, diversified structures and ability to treat ailments without creating undesired side effects provide strong candidacy of naturally occurring compounds for developing future drugs.

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