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TOTAL/DIVERSITY ORIENTED SYNTHESIS AND BIOLOGICAL EVALUATION OF NATUTRAL PRODUCTS: A CONCISE REVIEW

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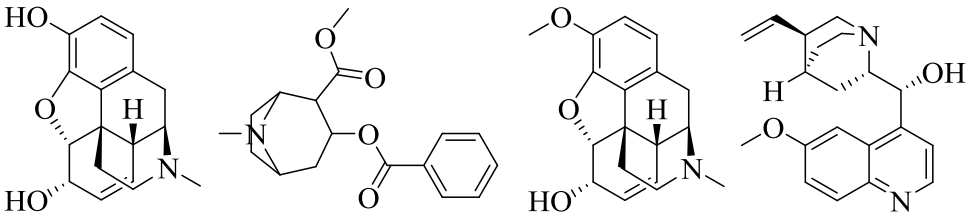
ABSTRACT

The human existence is insignificant in this world overwhelmed by terrible diseases; thus, one must learn from nature's agents to create new antidotes for the world's benefit. Medicinal herbs are a better source of these antidotes. Medicinal herbs have been used for healing since the dawn of time. The link between man and his search for drugs in nature extends back thousands of years, as evidenced by a variety of sources. Plants produce many secondary metabolites with a wide range of structures and functions. Natural product structures have a strong influence in other sectors, with the anti-infective field relying heavily on natural products and their analogues. The more effective use of natural products can be made through various derivatizations and modifications through drug development process which will later enhance the efficiency of lead compounds.

KEYWORDS: Natural products, Anticancer, Anti-HIV, Antibiotic.

1. INTRODUCTION

Throughout history, humans have relied on nature to provide them with food, housing, clothing, transportation, fertilizers, flavors, and scents, and, finally, but not least, medicines. For hundreds of years, plants have been the foundation of sophisticated traditional medicinal systems, and they are constantly offering people with novel therapies. In-spite of the unparalleled openings by medicinal chemistry, a significant source of drugs is the nature itself and continues to provide us with major compounds.[1] It all began with using plants in their crude form like teas, tinctures, powders, and various herbal formulations as medicines.[2] Over the time data of medicinal plants as herbs was documented. In recent times, the usage of plants as medicines evolved with the technique of isolating active ingredient, which began at first, with the discovery of morphine in the nineteenth century was isolated from opium.[3] Drugs like cocaine, codeine, quinine, etc. are early results of isolation of principal agents from medicinal plants.[4-6]



Morphine **Cocaine** **Codeine** **Quinine**

Fig.1.1: Some drugs derived from plants from early 19th century.

The diverse nature has provided us with ample sources for the cure of various diseases. An estimation of less than 10% of world's biodiversity is considered to have been studied as source of medicine. Despite the small fraction, humans have garnered vast benefits from bioactive natural products be it a molecule as small as the toxin of Dogger Bank itch to a complex molecule like, polycyclic compounds e.g., paclitaxel.[7-8]

Natural products (NP's) are the compounds of pharmacological importance, extracted from a living organism which contribute to a drug discovery or drug designing. From 2005 to 2007 alone, 13 drugs derived

from natural products received approval. Other drugs recently approved include compounds derived or isolated from sources like Semi-synthetic substances based on natural product templates, as well as plants, microorganisms, and animals.[9-11] For a millennium, the chemists & physicians have been motivated with the surplus source of medicinal agents in natural products. The high structural diversity & bioactivity has elicited the chemists to prepare these bioactive agents in laboratory. Many drugs that are used today are either natural products or derivatives of natural products.[12] The secondary metabolites of plant, animal or microbial origin can avoid many side effects of synthetic drugs because of their accumulation within living cells.[13] Irrespective of the competition from various other methods of drug discovery, there is still a good portion of trials for natural products especially in anticancer and hypertensive therapeutics. A recent finding by Newman, Cragg & Sander, showed that the drugs derived from natural products from1980 to 2002 among the total drug discovered were significant especially in anticancer &antihypertensive therapeutics.[14-15] Various examples exist which show us how the drug discoveries involving natural products are being used beyond their traditional usage in antimicrobial & anticancer agents. Herbal treatments have been studied in Alzheimer's disease and diabetic neuropathy models.[16] In a study by Proud foot in 2000, out of the small molecule drugs which were 29 in number, 8 were derived from natural products.[17] The various aspects of NP's are discussed in the following sections.

2. Research statistics on the modification of natural products

Products derived from nature (morphine from *Papaver somniferum*, vincristine from *Vinca rosea*, Taxol from *Taxus brevifolia* etc) have produced highly successful medications over the previous 100 years.An increment in the comeback of natural products being used as promising source of new medicine among the academicians and pharmaceutical companies. Fair shares of modern drugs (around 2/5th among the modern drugs) have been derived from natural products. Apart from this a success in past, natural products show a good scope in being the profit-oriented drug leads as well. The originality of the chemical nature of natural products is better than its alternative.[18] The future of therapeutics shall encompass the comprehensive study of natural products complemented by the ancient and modern therapeutic skills to emanate the maximum benefits out of both for the betterment of patients as well as the community in whole.[19] Synthesizing natural products can be done fully at an industrial level; however the structure of a natural product is too complex which results in its synthesis being expensive.[20] The World Health Organization (WHO) surveys, the sheer reality is that more than 1 billion people on earth live in extreme poverty and large masses are in dire need of not only safe drugs but cheap and affordable drugs, therapeutic agents and water. Keeping these things in view WHO has focussed its efforts for treatment of disease by limiting the number of essential drugs and pharmaceuticals and encouraging their use. Despite these rational efforts, reports suggest that half of the world's population still lacks access to these life-saving medications. Majority of the masses in developing countries are still dependent on conventional techniques. and folk medicine which is developed from medicinal plants for the basic health care.[21] Hence, comprehensive surveying, and modifying the secondary metabolites can be a fruitful exercise as has been seen in the drugs developed from natural product, e.g., Khellin to chromolyn and Podophyllotoxin to etoposide, etopophos and teniposide. Exploring nature for the therapeutics shall be rewarding. This thesis is an endeavour in extracting the therapeutic agents from medicinal plants, exploring their higher potential and lesser toxicity.

A literary survey where PubMed was used as a search engine revealed that approximately 1080 research papers are available on "natural products and their modifications in drug discovery" with promising results. In past decade a steady growth has been seen in the interest of researchers in this topic (**Fig. 1.2**).

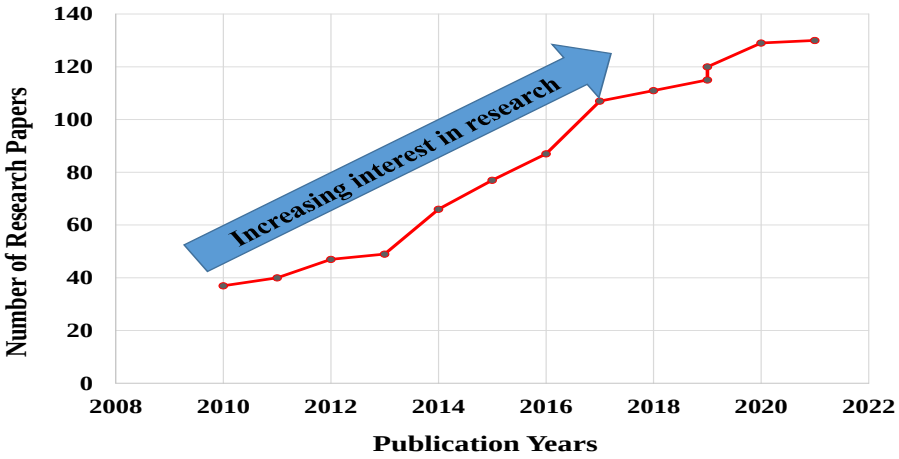


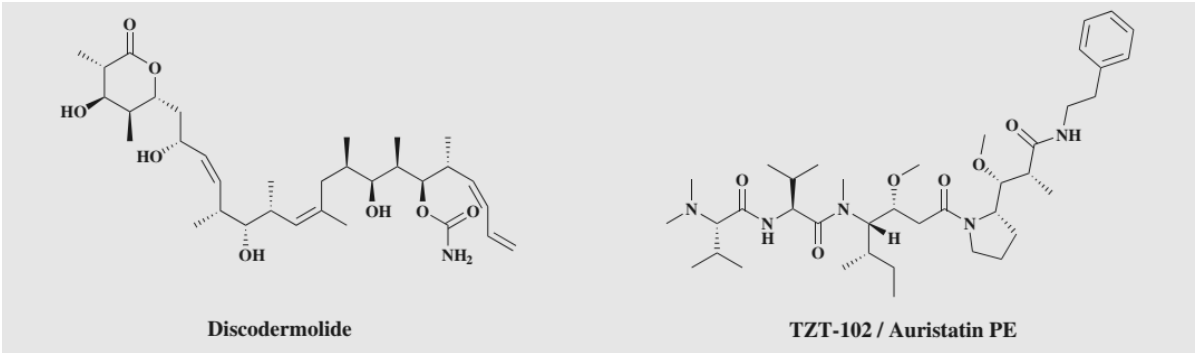
Fig. 1.2: A graphic representation of the increasing interest in research on the natural products and their modification from 2010 to 2020.

3. Approaches for the synthesis of Natural Products

3.1. Total Synthesis

Complex natural chemical synthesis in its entirety has been a major challenge for all of the world's leading synthetic chemistry groups, resulting in a significant boost especially at the turn of the twenty-first century and thereafter, to the area of organic chemistry. Nicolaou along his co-authors in 2000 expressed: "Total synthesis of natural products is now associated with the careful and tasteful selection of difficult and preferably biologically significant target molecules, the discovery and invention of new synthetic strategies and technologies, and chemical biology explorations through molecular design and mechanistic studies. Future advancement in the field is likely to be aided by advances in the extraction and characterization of novel molecular targets from nature, the availability of new reagents and synthetic processes, and information and automation technologies".[22] The original published structure has been revamped by total synthesis.Aworthy example being, diazonamide A,the marine-derived antitumor compound, (**Fig. 1.3**).[23-24] There has been a significant improvement in the synthesis of drugs as well as in modifying them that are as such strenuous to seclude in required amount for upgradation. During preclinical and clinical testing of various organically derived medications, adequate supply can be a major stumbling block. A favourable development for the clinicians running clinical trials as well as the patients is seen with the top synthetic groups focussing on developing an affordable synthetic strategy.A great example being the anticancer agent, marine-derived discodermolide (**Fig. 1.3**). Although the total synthesis showed significant quantities for clinical trials, however these trials were called off at PhaseI/II interface because of their poor aimed response and toxicity.[25-26] It has been seen that total synthesis leads to identifying a portion of sub-structural molecule, which might be that portion of the molecule necessary for a certain activity-pharmcophore, which, sometimes has even led to simpler analogues, wither better efficacy than its counterpart. In the case of halichondrin B, a marine-derived anticancer drug, total synthetic experiments demonstrated that the molecule's right half possessed the majority offeatures of the original product, as well as analogue "E7389". In 2010, the FDA gave its approval.[27] This entire synthesis, which took place in Massachusetts (USA), at the Research Institute Eisai, is most famous and remarkable creation of a completely synthesized therapeutic molecule in good laboratory practise (GLP) and later under present manufacturing conditions practises (cGMP). Before finalizing the compound which later got to be called eribulin (Halaven®) almost 200 derivatives were made. Despite the lack of a formal publication, anecdotal sources suggest that the final commercial product's usage of repeated crystallisation over chromatographic separations was inherited during the scale-up process. Thecontinuous work of Eisai Research Institute of Natural Products from the aquatic life, with the major successes of laulimalide's total synthesis and other simpler compounds like E-7974 (**Fig 1.3**) that are fundamentally the modified tripeptide, hemiasterlin. Total synthetic analogues have continue to develop even though there have been instances with the original natural product clinical trials failing.Perhaps this is why clinical trials on anticancer drugs derived from the sea, such as "dolastatin 10 & dolastatin 15", were stopped, while dolastatin 10's synthetic analogues, TZT-1027 (auristatin PE or soblidotin; Fig. 1.3), were promoted as "lease on life" by connecting the peptide, with a small alteration (auristatin F, Fig. 1.3), employing a particular antibodythat are tumour specific scission.[28] Compounds mostly synthesized in "more than milligram quantities" as done on peloruside by Paterson groups (at Cambridge University)[29], improvising therapeutic agents from marine and plant sources, such as including dictyostatin[30], and more broad issues to consider polyketide syntheses[31] are all examples of familiar accomplishments in synthesis of compounds from marine sources.

Another example is the synthesis of spongiostatin **1** on a 1gram scale at the University of Pennsylvania by the Smith group.[32] These are a few recent examples of creative chemical approaches paired with novel reactions, sometimes known as "one-pot" synthesis or Baran's pioneering biomimetic synthesis using minimal protecting groups.[33]



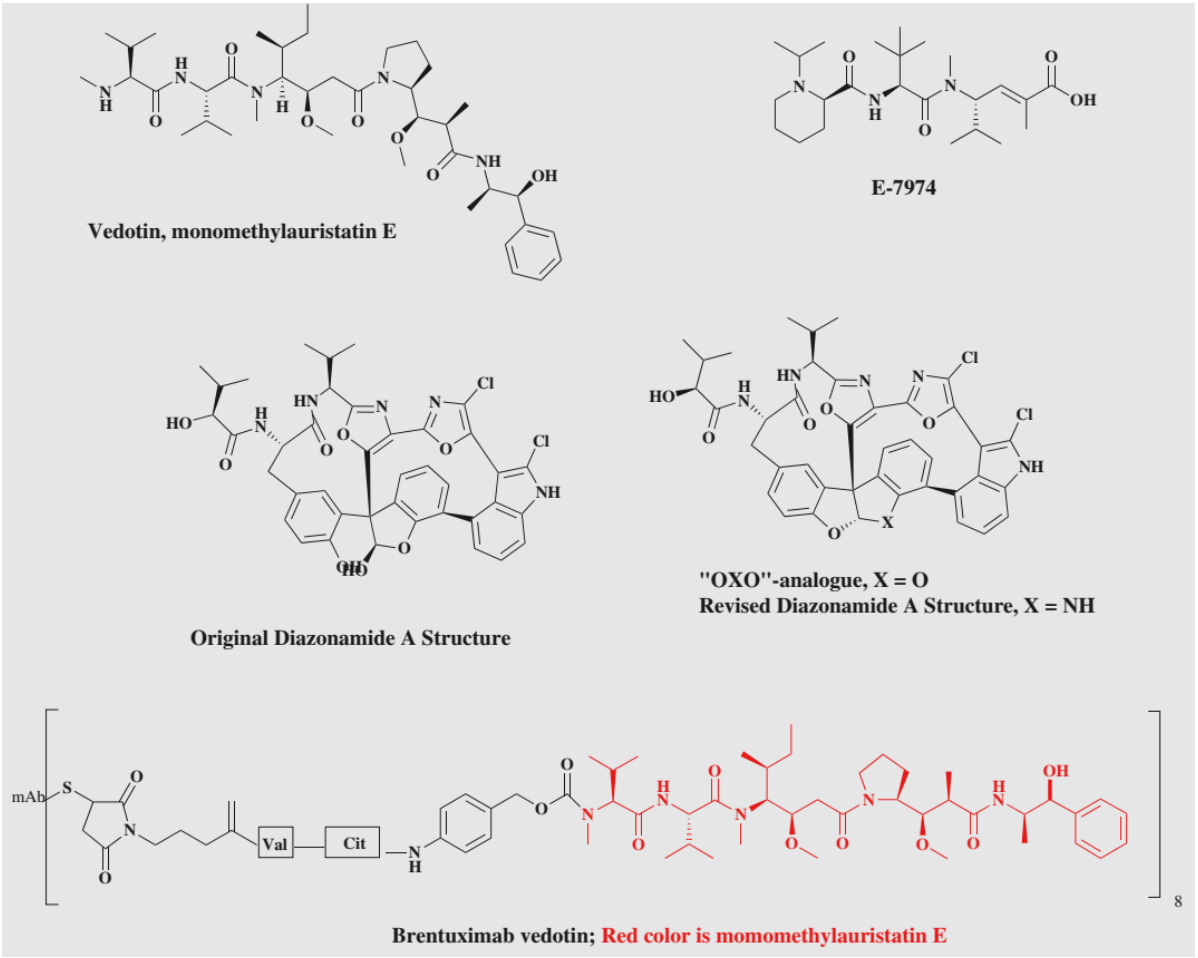


Fig. 1.3: Privileged structures of total synthesis approach.

3.2. Diversity-Oriented Synthesis

Previously used, parallel synthetic approach, where a natural active product is utilised as a central scaffold, providing enough analogues for the study of structural activity. That can be illustrated in the sarcodictyin production (**Fig. 1.4**).[34] The further illustration of the idea of "privileged structures" signifies the importance of combinatorial chemistry (methods that enable the process of preparing a huge number of compounds in a single step)[35] and various groups have successfully developed it.[36] A literature search turned up over 4,000 moieties of 2,2-dimethyl-2H-benzopyran (Fig. 1.4), with an extra 8000 structures discovered by simply changing the search parameters. Benzopyran with cyanostilbene discovery and optimization is achieved by the methods like solid-phase synthetic methods (**Fig. 1.4**) which gave effective results against bacteria that were previously resistant to Vancomycin.[37-39] Contrary to the claims that combinatorial chemistry produces new leads[40], decline in the new NCEs[41] shows that there is decline in the drug discover using combinatorial chemistry seen in past 10 years, and the libraries being said to be as "poorly designed, impractically large, and structurally simplistic".[42] "In industry, a more methodical strategy based on arrays of fewer, well-characterized chemicals has largely replaced an initial emphasis on producing combinations of very large numbers of molecules," according to the article, with "a special push toward the synthesis of complicated natural-product-like compounds – molecules that are structurally similar to approved natural-product-based medications". "Rescuing Combichem" was another essay that stressed the use for the generation of combinatorial libraries using natural product-like scaffolds. DOS aspires to continue where classical combinatorial chemistry left off".[43] "The natural product-like molecules synthesized in DOS have a considerably higher opportunity at connecting with desired molecular targets and exhibiting intriguing biological activities," according to the article. In 2009, Cragg *et al* reviewed and gave a brief discussion on the different chemical methods and the relative difference in between them[44] and in 2011 Waldman presented an excellent deliberation on BIOS system[45], that should be read along with the deliberation of "Chemical Space with Natural Products," which was also published in 2011.[46] Schreiber group intensified the production of natural-product-like libraries, which amalgamated the skeletal information elements and latent intermediatesin the production of above 1000compounds of structural importance and diverse chirality.[47-48] With complete examination and investigation of skeletons of active natural products, apparently simple and basic precursor molecules can be isolated which can act as the founding blocks in combinatorial synthetic schemes, thus

permitting us to investigate the structural activity. The molecules like dysidiolide, galanthamine and psammaplin that have been formed using the solid phase synthesis of molecules (**Fig. 1.4**), have been reviewed.[49-52] Tan[53] and Quinn[54] groups work on the recent natural product can be seen.

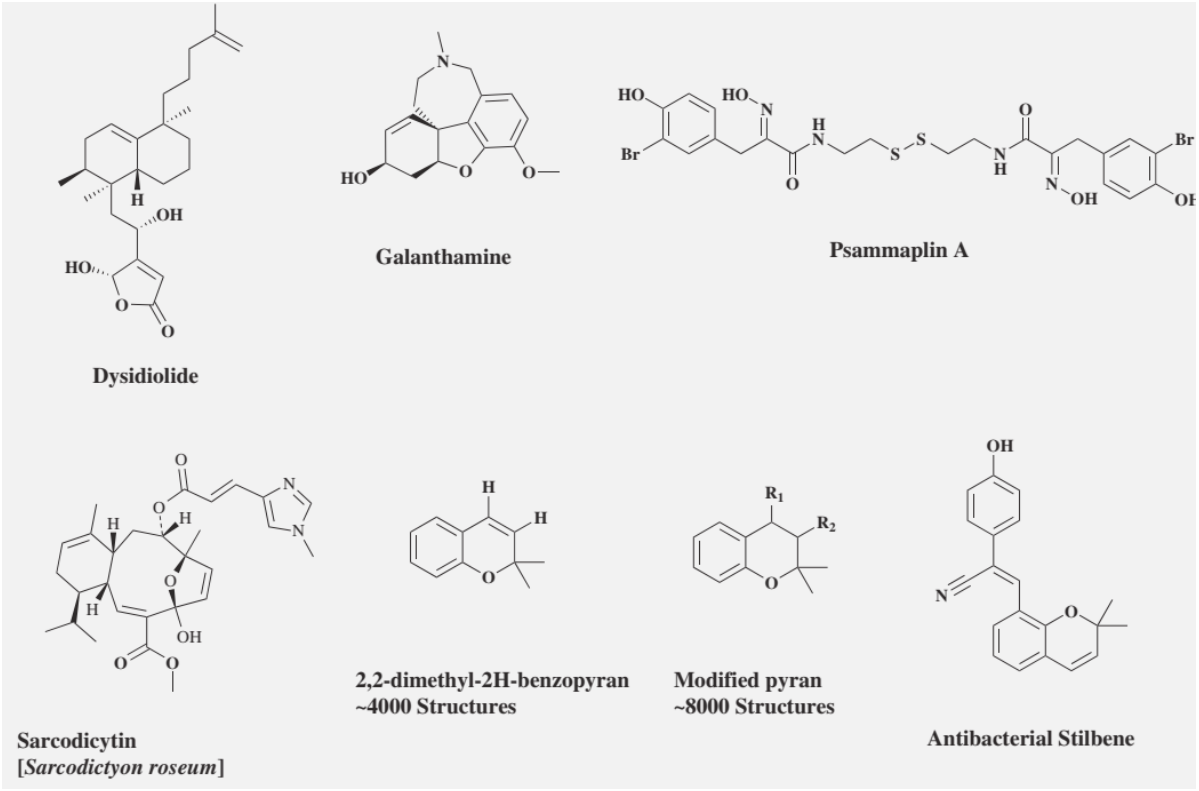


Fig. 1.4: Privileged Structures from diversity-oriented and parallel synthesis approach.

4. Biological applications of natural products

Since many novel drugs have origins from natural products, one would predict that big pharma companies would consider natural products as the major element in drug discovery strategy. But it turns out; the Big Pharma companies have either scaled down or have terminated screening natural resources. This is because natural resources are regarded to be unsuitable for modern High Throughput Screening (HTS). In addition, with the goal of reaping large in terms of rewards of many innovative medications; mass-produced Combinatorial Libraries are being screened. The imminent human gene's structure and the need for large production of new targets have made the work more exciting and interesting in the present times. The core framework was that the combinatorial chemistry would produce millions of compounds, that when screened by HTS, would eventually result in drug leads due to the sheer increase in quantity. And henceforth would in lesser time would yield greater no of therapeutic agents than the traditional way of drug discovery methods. Subsequently the research of natural products was hampered. Theobvious increase in the production, however, hasnot so far transpired. Despite this baffling decision to downscale natural products' position in medical research in favour of a less dependable discovery platform, an unequal number of New Chemical Entities (NCEs) based on natural products or natural product derived scaffolds have been approved in the recent decade. Natural products play an essential role in medication development, which can be seen or felt in major therapies. Natural goods have been of major importance and have proven to be beneficial on occasion when synthetic compounds have failed to provide. The following are some of the benefits of natural goods in therapeutics and other fields.

4.1. Naturally Products as Anticancer Agents

Natural products are highly considered for the cure of various carcinomas and are preferred over synthetic compounds because of their high specificity and less side effects.[55] In last 20 years there are enough evidence which suggest that half of the anti-cancer drugs have had their source as natural products are registered by US FDA.[56-58] Among these natural products major portion is constituted by the heterocyclic compounds. Theheterocyclic molecules which are mostly of clinical importance are "paclitaxel", "docetaxel",[59] "taxol",[60] "camptothecin",[61] "combretastatin",[62] "epipodophyllotoxin",[63] and "vinca alkaloids".[64] Cancers such as leukemia, advanced testicular cancer, breast, lung, and Kaposi's sarcoma are all treated with these heterocyclic natural compounds.[65] In chemotherapeutic agents Epothilones (16-membered cyclic macrolides) created a name for itself due to its positive results in various clinical trials.[66] There are

around 175 heterocyclic anticancer medicines on the market and in clinical studies. and 85 of them are from the natural origin. These cancer-fighting substances which occur naturally have been extracted or derived from mostly sea population, plants and microbes.[67-70]

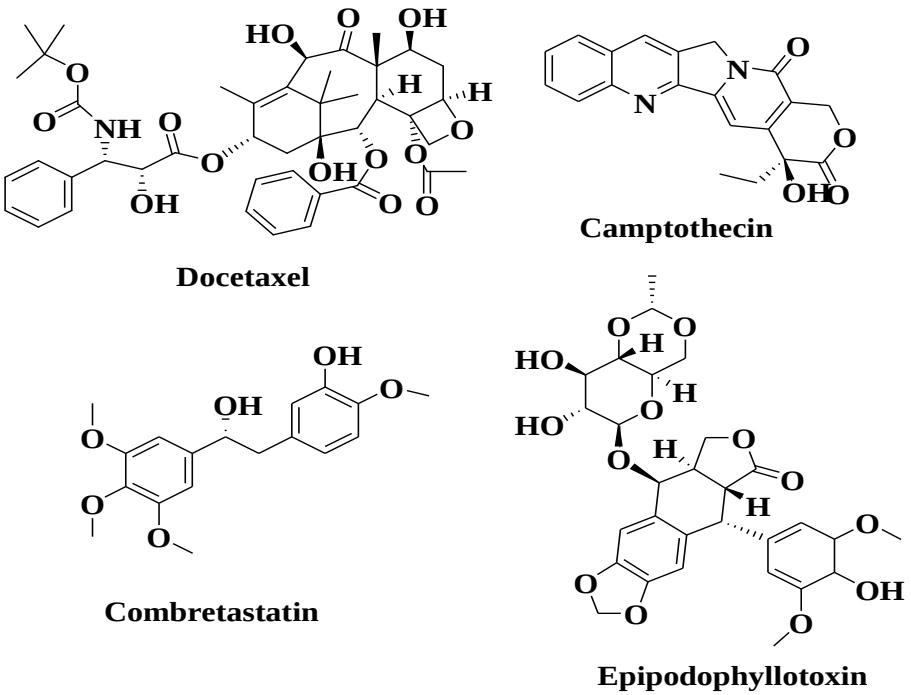


Fig. 1.5: Chemical structures of some natural products as anticancer agents.

4.2. Natural Products as Antibiotic agents

Popular antibiotic agents of our daily life belong to the customary natural product classes, that consists of β-lactams (penicillin and cephalosporins)[71], macrolides (erythromycin)[72], aminoglycosides (streptomycin)[73] and glycopeptides (vancomycin).[74]

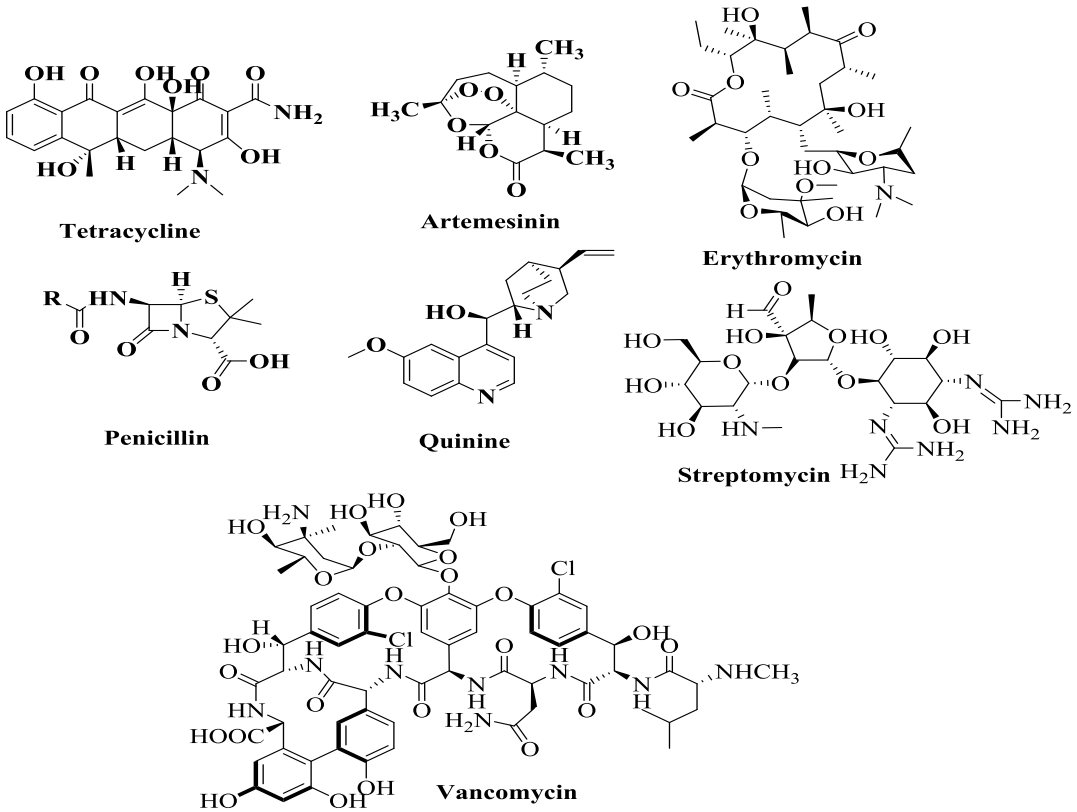


Fig. 1.6: Chemical structures of some natural products as antibiotic agents.

4.3. Natural Products as Central nervous System Based Agents

Among the CNS-active drugs of clinical importance, several of them are derived from natural products. Most popular example being thenaturally occurring yohimbine alkaloid reserpine.[75] Reserpine is a medication that is used as an antihypertensive, a tranquillizer, and most recently as an active multidrug efflux pump inhibitor of Gram-positive bacteria including Mycobacterium tuberculosis (MTB).[76] Similarly, galanthamine41, which was originally derived from Galanthus nivalis, has recently been approved for use in the treatment of Alzheimer's disease. Among many more examples, Cabergoline[77], A long-acting dopamine D2 receptor agonist is a medicinal drug generated from natural products that is used in Parkinson's disease treatment. It is the counterpart of ergot alkaloid that occurs naturally, it's an active molecule of the group whose members have lysergic acid in them.[78]

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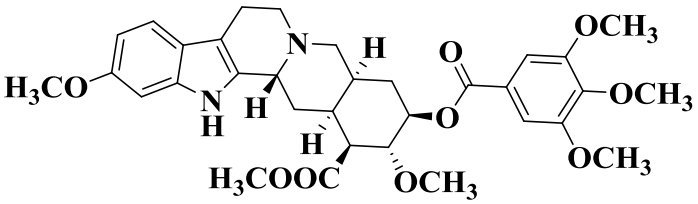
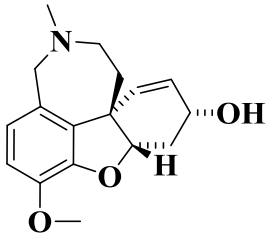
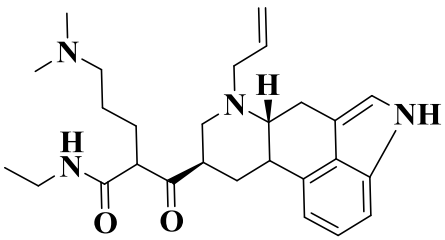


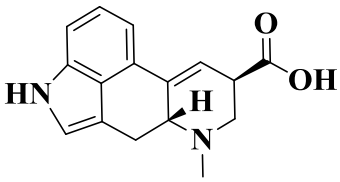
Reserpine



Galanthamine



Cabergoline

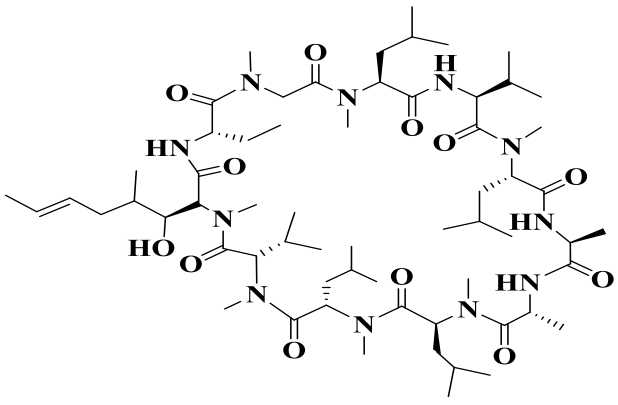


Lysergic acid

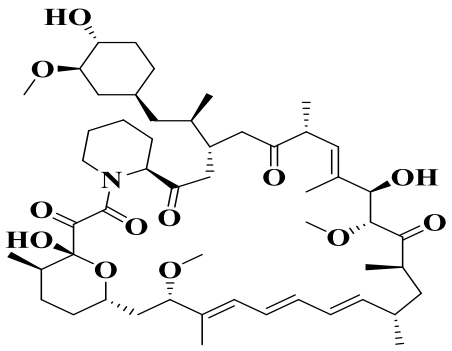
Fig.1.7: Chemical structures of some natural products as central nervous system-basedagents.

4.4. Natural Products as Immuno-modulating Agents

Along with all the above applications even the immunosuppressive agents showed to have connections with the natural products. A naturally occurring immunosuppressive like cyclosporin A has shown significant increase in the better prognosis of organ transplantation.[79] And in recent times rapamycin, the naturally occurring product is in the market as an immunosuppressive drug, for better prognosis in organ transplantations.[80]



Cyclosporin A



Rapamycin

Fig. 1.8: Chemical structures of some natural products as immuno-modulating agents.

4.5. Natural Products as Anticholesteremic Agents

It's broadly accepted that the statins, inhibitors of the HMG (3-hydroxy-3-methyl-glutaryl) CoA reductase, are active as anticholesteremic agents. Long term cardiotonic benefits are believed to exist.[81] Products derived from nature viz *Penicillium brevicompactin*, *Nocardia autotrophica* and *Aspergillus terreus*, are mavastatin (compactin), pravastatin (pravachol), and lovastatin (mevacore) respectively. Simvastatin (zocor) is a semisynthetic derivative that is similar to lovastatin in structure. This class of semi synthetic statins includes atorvastatin (lipitor), a megablockbuster medication.[86]

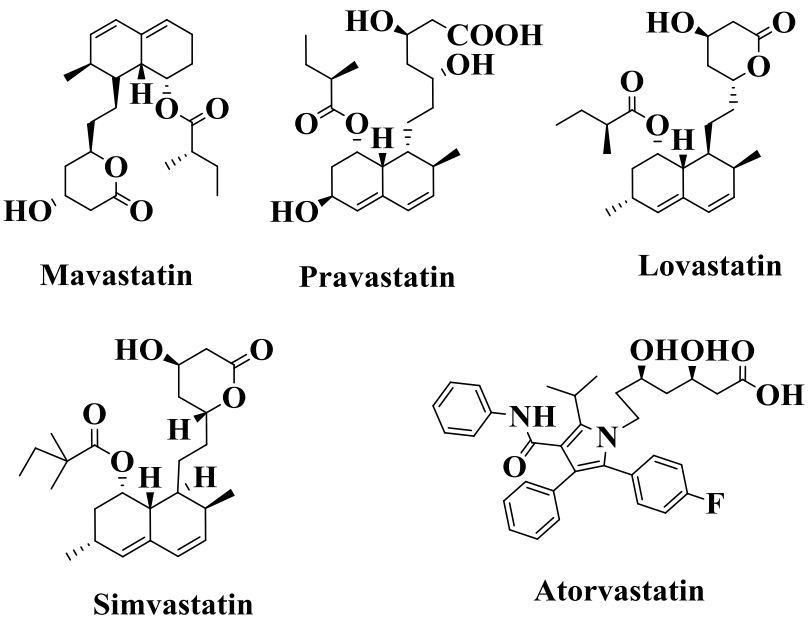


Fig.1.9: Chemical structures of some natural products as anticholesteremic agents.

4.6. Natural Products as Anti-HIV Agents

Despite the Major advances, the disease "acquired immunodeficiency syndrome" (AIDS) affects the immune system and central nervous system of a human body still exists as an iirremediable enormous health issue. Although over the past few years we have widened our Treatment options, with 19 synthetic drugs getting approval to be used clinically in the United States. But these synthetic drugs come with extreme toxicities that can range from suppression of bone marrow, anemia, and peripheral neuropathy. Along with this, the required dosages are complex, making it hard to maintain them. Then the high pricing of such drugs makes its use even more limited especially in countries where the disease is more prevalent and the affected population being mostly poor like developing countries. New Partners Initiative (NPI) in the United States and other research centers are working tirelessly to address HIV drug development difficulties. The investigation of plant extracts resulted in the extraction of many chemicals having anti-HIV activity.[86]

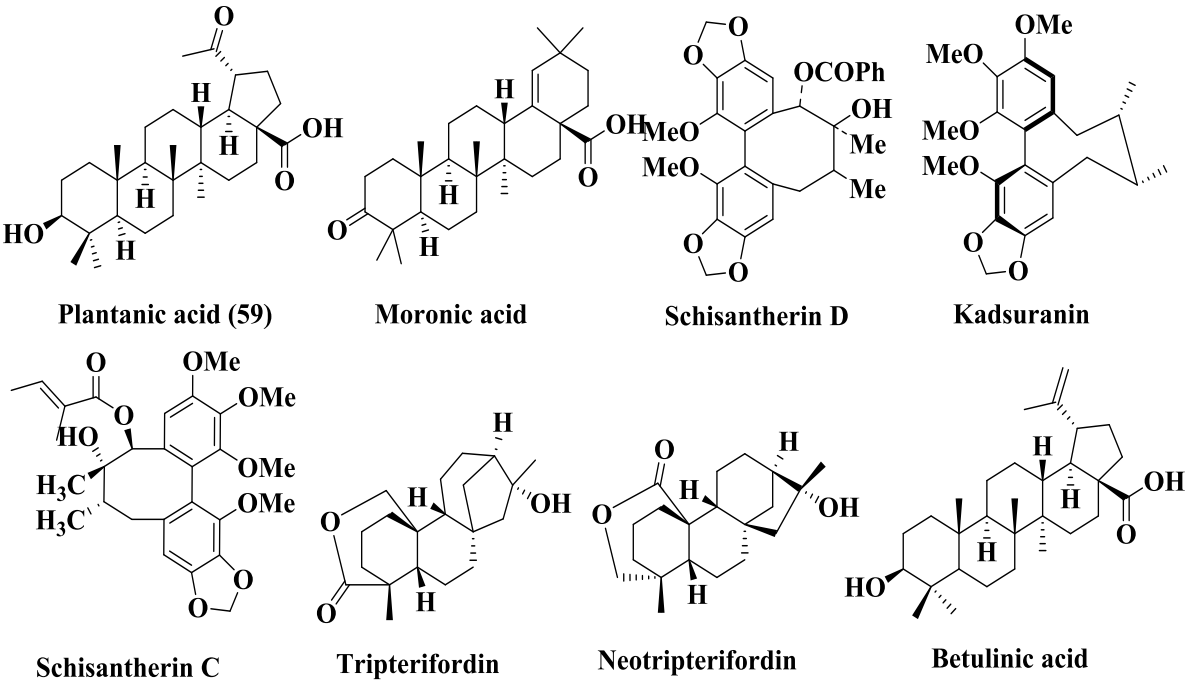


Fig. 1.10: Chemical structures of some natural products asanti-HIV agents.

CONCLUSION

The renaissance of plant-based medications, as evidenced by the growing number of clinical studies is clearly promising, particularly as a therapy for cancer, immunological, and CNS-related illnesses. Prostratin, CAPSOROLS and CCS are just a few of the innovative plant-based therapeutic candidates in current preclinical trials. By combining traditional medical expertise with new tools to accelerate plant-based drug development, scientists have been able to conduct a comprehensive and exhaustive study on plants, extending beyond the 10–15 percent of plant diversity that has been investigated thus far for pharmaceutical purposes. We still have a long way ahead to explore theplants, discover the various therapeutic agents that nature has bestowed us with to cure the mankind from various diseases. More than 60 compounds for anti-cancer drugs are under trial, which have their origins from plants. And in the course of time, it's going to remain an engrossing area of diseases and its cure.[87] Statistics suggest that a few 90,000 chemicals derived from natural sources and those synthesized via total synthesis in development of drugs contribute 40% of all conceivable novel therapeutic molecules. While the remaining 60% contribution comes from millions of synthetic molecules.[88] This exceptionally prominent difference in the productivity of natural compounds over synthetic is attributed to the verity that nature has pre-selected compounds that effect the specialised metabolism of living organisms, but manufactured molecules have no such benefit.[89] Natural products are still playing a significant role, an important role in the development of novel structural entities for medication development, despite the pharmaceutical industry's significant investments in Drug discovery technology in the current era such as combinatorial chemistry and Robotic-based High-Throughput Screening. The separation of compounds from natural resources has resulted in the identification of new pharmacological action mechanisms.[90]

Natural products and their derivatives are distinctive and are biologically sound as their co-existence and co-evolution with target sites in biological system. Indeed, the discovery for natural products is very strenuous, tedious as well as challenging as the process of isolation, purifying and structure elucidation endeavours more patience for recognising good effective compoundswith the arrival of hyphenated instrumentation like LC-Mass-NMR and dereplication process has augmented the extracts quicklyand these ways are becoming popular in the current drug discover platforms. Data base searching can be used to perform dereplication. However, there is a lot of room for new ideas to examine the diverse range of NP biodiversity, including cell-based and biochemical assays. Natural products will continue to be at the forefront of drug development in the future. If history is any indication, there will surely be many more unique and stronger physiologically active natural products discovered in the future.

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