Chapter - 1

Natural products and their role in drug development
Natural Products and Their Role in Drug Development: A brief overview

1. Introduction

"There are many things between heaven and earth..." despite the progress of science during the past four centuries, Shakespeare’s words have not lost their originality. Knowledge about the etiology of diseases is still limited, and for many life-threatening diseases, like cancer, tuberculosis, AIDS, diabetes, etc., no effective treatment exists. Nature has always been a valuable source of drugs and afford unprecedented opportunities for medicinal chemistry to continuously deliver the lead compounds. In the form of her vast repository (photo-biodiversity), Mother Nature has provided a complete store house of remedies to cure all ailments of mankind. Natural products derived from plants, animals and minerals have been the basis of treatment of human diseases for thousands of years. Among them, plants have been of great potential for producing new drugs for the great benefit to human kind. Plants have afforded a rich source of compounds that have found many applications in the fields of medicine, pharmacy, and biology.

Human beings have been using plants as medicines since Middle Paleolithic age, some 60,000 years ago. According to the World Health Organization (WHO), almost 65% of the World’s population have made natural products as the first defensive tools for the treatment of many diseases. A large number of natural products, especially plant-derived drugs, continue to be discovered on the basis of traditional or empirical local medical practices. Use of plants in the traditional medicine systems dates back to era of Mesopotamia, Egypt, Greece, Rome, China, India and many other cultures. Natural products are still considered a valuable source of drug leads, and testing of extracts is widely practiced in the pharmaceutical industry. Natural products from botanical sources used in traditional medicine may combat multidrug-resistant (MDR) infectious diseases through the elucidation and validation of biological compounds with novel mechanisms of action.

There has been a remarkable renaissance of interest in natural product research over the last decade and is enjoying renewed attention for providing novel and interesting

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1 Solecki, R.; Shanidar, IV. Science, 1975, 190, 880.
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scaffolds. Outstanding developments have been stepped up in the area of separation science, spectroscopic techniques, and micro-plate based in vitro assays. The various hyphenated techniques, e.g., GC-MS, LC-PDA-MS, LC-MS-MS, LC-FTIR, LC-NMR, LC-NMR-MS, CE-MS, have made possible the pre-isolation analysis of crude extracts or fractions from different natural sources as well as isolation and on-line detection of natural products, chemotaxonomic studies, chemical finger printing, quality control of herbal products, dereplication of natural products and metabolomic studies.

Structural modification of natural products has become an integral part of the drug discovery process. Many potential drugs and lead compounds derived by structural modification of natural compounds, or by the synthesis of new compounds, have been designed following a natural compound as a model. In modern methods of drug discovery processes, design and synthesis of drugs based on the biological targets is of the great interest to modern medicinal chemists. The huge structural diversity of natural compounds and their bioactive potential have meant that several products isolated from plants, and for that reason also from marine flora and microorganisms can serve as "lead" compounds for the improvement of their potential therapeutics effected by molecular modification. Additionally, semi-synthetic processes for new compounds, obtained by molecular modification of the functional groups of lead compounds, are able to generate structural analogues with greater pharmacological activity and with fewer side effects. The new structural analogues after chemical modification of a natural product gives inputs to medicinal chemists to study their structure-activity relationship (SAR). SAR is an important aspect of a drug to understand its medicinal properties and mechanism of action or pathway.

Since the drug discovery process is an intense, lengthy and interdisciplinary endeavor, this process has been revolutionized with the advent of genomics, proteomics,
bioinformatics and efficient technologies like, combinatorial chemistry, high throughput screening (HTS), virtual screening, de novo design, in vitro, in silico ADME(T) (Absorption Distribution Metabolism Excretion Toxicity) screening and structure-based drug design. Computational tools offer the advantage of delivering new drug candidates more quickly and at a lower cost. Among these computational techniques, rational drug design with in silico approach have good application capabilities towards drug discovery. In silico methods can be used to analyze the target structures for possible binding/active sites, to generate candidate molecules, to check for their drug likeness, to dock these molecules to the target, to rank them according to their binding affinities, further, to optimize the molecules to improve binding characteristics. Structural modification of a bioactive natural product for better lead molecule or candidate can be gratified with rational design of structural analogues using in silico docking methods.

2. Natural products as drugs from folklore approach and traditional systems

Historically, ethno-pharmacology was the origin of all medicines and plant products were the most important sources of drugs. This knowledge of drugs 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. In pre-industrialized society and in agrarian societies, plant-derived natural products were used by indigenous population as therapies for many diseases ranging from infections to emphysema. On numerous occasions, the folklore records of many different cultures have provided leads to plants with useful medicinal properties.12,13

Toxin (1)

Paclitaxel (2)

It has been estimated that less than 10% of World’s biodiversity has been studied seriously as source of medicines.14 Yet, from this small fraction, humanity has reaped

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enormous benefits in the form of bioactive natural products that span all the way from small molecules such as the toxin (1) responsible for Dogger Bank itch\textsuperscript{15} to a complex, polycyclic compounds such as paclitaxel (2). A remarkable galaxy of pure compounds with different pharmacological activities has been isolated from natural sources.\textsuperscript{16,17,18} A sampling of some of these natural products bearing novel chemical scaffolds (including compounds 3-12 of historic interest) are shown in Figure-1.

![Chemical structures of natural products](image)

**Figure-1**

Mankind is grateful to plant kingdom for some of the useful drugs like vinblastine (10) and vincristine (12), isolates of the African periwinkle, *Carthamus roseus* (Apocynaceae) for their use in treatment of pediatric leukemia and Hodgkin's disease.\textsuperscript{19} Despite competition from other drug discovery methods, natural products are still providing

\textsuperscript{18} Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* 1997, 60, 52-60.
their fair share of new clinical candidates and drugs, especially in the anticancer and antihypertensive therapeutic areas. Clinical, pharmacological, and chemical studies of the traditional medicines, derived predominantly from the plants, have been the basis of most early medicines such as pilocarpine (7), aspirin (13), morphine (15), quinine (16), and digitoxin (17) (Figure-2).

Aspirin (13) that bears a very simple chemical structure is a powerful synthetic drug used to treat a wide variety of ailments, more so as an anti-inflammatory drug, and a pain reliever. The natural product that provides the basis for aspirin is salicylic acid, which is isolated from the bark of the willow tree. Use of the willow tree for medicinal purposes dates back nearly 2500 years (to the time of the ancient Mediterranean empires). One of the side effects of salicylic acid is gastric discomfort and irritation, but a small modification in the form of the preparation of its acetyl derivative (aspirin) partially reduces the side effects to use it as a therapeutic agent. Aspirin (13) also functions as an important preventative treatment against heart disease because of its inhibition of prostaglandins, which affect the clotting of blood.

Codeine (14) and morphine (15) are two other well-known analgesics. Both of these similarly

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structured alkaloids come from unripened seedpods of the opium poppy plant.\textsuperscript{24} Use of morphine (15) as a drug dates back many centuries to a time when monks saw the anesthetic and pain-relieving properties of \textit{Papaver somniferum}. While codeine is less effective in its pain-relieving abilities than morphine, it is also used as a cough suppressant, and a considerably less addictive drug, producing fewer effects of euphoria as compared to its narcotic cousin.\textsuperscript{25} In spite of side effects and the possibility of addiction, morphine (15) remains one of the most powerful and effective medicines for the reduction of intense pain in clinical situations, an advantage that cannot be matched by any human made compound.\textsuperscript{26}

Quinine (16), obtained from the bark of the Cinchona trees, is one of the oldest of a number of anti-malarial drugs that are currently available. Throughout its history, quinine has perhaps saved more lives than any other drug.\textsuperscript{27} Digitalis comes from \textit{Digitalis purpurea}, a large flowering herb native to Great Britain. The leaves of this plant produces digitoxin (17) (another name for digitalis), a glycoside prescribed for heart failure and irregular heart rhythm, as well as digoxin (11), a kidney diuretic, both of which are toxic at high concentrations.\textsuperscript{28} Alkaloid Pilocarpine (7) extracted from the Jaborandi tree (\textit{Pilocarpus jaborandi}) is used as a weapon against the blinding disease \textit{glaucoma}.\textsuperscript{29}

In Andean culture, the leaves of the coca tree have been primarily chewed to obtain perceived benefits. From ancient times, indigenous people have added alkaline materials such as crushed seashells or burnt plant ashes to the leaves in order to accentuate the pharmacologically active moieity of coca. In 1860, a German chemist Carl Koler isolated cocaine, the chemical responsible for the biological activity. He found that cocaine could act as a local anaesthetic in eye surgery. As the years passed, scientists observed that cocaine paralyzed nerve endings responsible for transmitting pain. As a local anaesthetic, it revolutionized several surgical and dental procedures.
American Indians on the island of Guadeloupe used pineapple (*Ananas comosus*) poultices to reduce inflammation in wounds and other skin injuries, to aid digestion and to cure stomach-ache. In 1891, an enzyme that breaks down protein (bromelain) was isolated from the fresh juice of pineapple and was found to break down blood clots. Other pharmaceuticals that have their origin in traditional medicines include Artemisinin (18) (Quinghaosu), the antimalarial sesquiterpene from a Chinese medicinal herb *Artemisia annua* used in herbal remedies since ancient times, Forskolin (19) the anti hypertensive agent from *Colens forskohlii* Briq. (Labiatae), a plant whose use has been described in ancient Hindu Ayurvedic texts, Reserpine (20) (from *Rauwolfia serpentina*) for high blood pressure, Piperene (from *Piper species*) as bioavailability enhancer, Curcumin (21) (from *Curcuma longa*) in inflammation, and Withanolide A (22) (from *Withania somnifera*) as immunomodulators. Modern searches for bioactive molecules typically make use of sophisticated bioassays and bioassay-guided fractionation of medicinal plants used by traditional healers. This has led to the isolation of several new therapeutically important compounds. A recent example is the medicinal tree *Homolanthus nutans* (Euphorbiaceae), used by Samoan healers to treat yellow fever, a viral disease. Working on this plant, a team of researchers from National Cancer Institute (NCI) USA, discovered that its extract exhibit anti-HIV activity. Bioassay-guided fractionation resulted in the isolation of Prostratin (12-deoxyphorbol 13-acetate, 23) an active compound which was found to stop cells from becoming infected with HIV-virus and prolong the life of infected cell. Currently, NCI is considering Prostratin (23) as a potential candidate for drug development (Figure-3).

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H3CO Forskolin (19)

Reserpine (20)

Curcumin (21)

Withanolide A (22)

Prostratín (23)

Figure 3

3. Role of structural modification of natural products and their mimics in drug discovery

Natural products (NP’s) continue to represent an excellent source for lead structures for drug discovery. There are only few cases, where NPs serve directly as drugs, but many of the drugs are the structural analogues and or mimics. For a better drug or lead compound, the molecule should possess not only high potency but also contain other properties like being non toxic and with efficient ADME (Absorption, Distribution, Metabolism, Excretion). To address to these issues, structural modification of NPs has been undoubtedly playing pivotal role for the development of efficient modern medicine. Structural analogues of natural products can give inputs for the clear picture of molecular mechanistics to a medicinal chemist.

Literature is full of examples wherein the modification of a natural product has led to a drug with optimized or minimized toxicities, better drug delivery or higher potency. Khellin (24) was initially used as bronchodilator but found to cause nausea and vomiting. Chemical modification of Khellin (24) led to chromolyn (25) (used as sodium chromoglycate), which enabled the drug to stabilize cell membrane in the lungs to prevent

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the allergen induced release of substance ultimately seen as a cause for bronchoconstriction in allergic asthma patients.

![Diagram](Figure-4)

Similarly, modification of natural product papaverine (26) led to verapramil (27) a drug to treat hypertension. Galegine (28) isolated from *Galega officinalis* provided template for the synthesis of Metformin (29) an anti-diabetic drug. (Figure-4)

Based on the observation that a nonapeptide (Glu-Try-Pro-Arg-Pro-Glu-lie-Pro-Pro) from *Viper venom* caused lowering of blood pressure, new hypertensive agents were developed which are known by trade name “Prils” like Captopril (30), Enalapril (31), Lisinopril (32), Cilazapril, Spirapril. These constitute one of the most important class of cardiovascular drugs. Likewise, drugs have been developed which involve synthetic molecules/materials from agents originally derive from plants. For example, Psuedoephedrine (33), originally derived from *Ephedra sp.*, has been a model for the preparation of new synthetic drugs like Propronalol (34), Metaprolol (35), Atenolol (36), etc., (Figure-5). These drugs are also known as natural mimics. The above examples proves

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clearly that the structural modification of natural products has a greater role in Drug Discovery.

![Figure-5](image)

4. Natural products and their derivatives as drugs - Current status of natural products research

Chemical substances derived from animals, plants and microbes have been used to treat human disease since the dawn of medicine. Given that NPs have historically provided many novel drug leads, one would assume that NPs would still play a pivotal role in the drug discovery strategy of Big Pharma companies. The investigation of natural products as source of novel therapeutics reached its peak in the Western pharmaceutical industry in the period 1970–1980, which resulted in a pharmaceutical landscape heavily influenced by non-synthetic molecules. Out of 877 small-molecule as New Chemical Entities (NCEs) introduced between 1981 and 2002, nearby half (49%) were natural products, semi-synthetic natural product analogues or synthetic compounds based on natural-product pharmacophores. Despite this success, pharmaceutical research into natural products has experienced a decline for a decade or two and most of the Big Pharma companies terminated or significantly scaled down screening natural resource collections because these studies thought not to fit into modern High Throughput Screening (HTS) strategies coupled with the expectation that screening mass-produced Combinatorial Libraries would result in reaping rich rewards in terms of a multiplicity of novel drugs. The basic premise of this expectation was that combinatorial chemistry would generate libraries consisting of millions of compounds, which
would be screened by HTS and produce drug leads by sheer weight of numbers. The leads would be delivered in quicker time and in greater numbers for all therapeutic areas compared to traditional drug discovery methods, and as a consequence, NP research took a back seat. The impending structure of the human genome and the promise of a plethora of new targets added to the excitement of the time. The expected surge in productivity, however, has not materialized. Despite this puzzling (and seemingly disastrous) decision to significantly downplay the role of natural products in Medicinal research in favor of far less validated discovery platform, a disproportionate number of new chemical entities (NCEs) approved even over past 10 years have in fact been natural products or natural product-based. The impact of natural products on drug development can be felt across virtually in every major therapeutic area. Facts and figures about natural products with relation to the drug discovery have been well represented in the review articles by Newman and Cragg over the period 1981 to 2008. Contribution of NPs towards drug discovery is depicted in the Figure-6, which enlists the NCE’s introduced during the period 1981 to 2008.

It is interesting to see that, in a list of 1024 NCE’s, 6% are pure natural products (N), 27% natural modified molecules (ND), 13% contribution is from synthetic compounds showing competitive inhibition of the natural substrate (S/NM), 17% from synthetic

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compounds with a natural product pharmacophore (S*) or a natural product pharmacophore showing competitive inhibition of the natural product substrate (S*/NM), and only 37% are synthetic compounds that are derived of any natural product concept. In nutshell, the figure shows 63% drugs of the NCEs are from NPs, moreover 80% drugs which have been in use for cancer therapy are of natural products only. The above discussed NCEs are contributing to various class of drugs such as antimalarials, antibiotics, anticancer and other therapeutic areas. Where ever lead compounds from synthetic libraries have failed to deliver, natural products have proven their worth. In the following sections the role of natural products in different therapeutics and other areas of importance are illustrated:

4.1. Antibiotic agents

Many of the most prevalent antibiotic agents used in today’s life belong to the members of well-known natural product classes, including \( \beta \)-lactams (penicillin’s, carbapenems and cephalosporins, 37), \(^n\) macrolides (erythromycin, 38), \(^a\) aminoglycosides (streptomycin, 39) \(^b\) and glycopeptides (vancomycin, 40), \(^c\) (Figure-7).

\[ \text{Cephalosporin (37)} \]
\[ \text{Erythromycin (38)} \]
\[ \text{Streptomycin (39)} \]
\[ \text{Vancomycin (40)} \]

Figure-7


4.2. Central nervous system-based agents

A number of clinically important CNS-active drugs are readily traceable to natural sources (Figure-8). Notable examples include the naturally occurring yohimbine alkaloid reserpine (41).53 Reserpine (41) has found application as an antihypertensive agent and a tranquilizer and of late as an active multidrug efflux pump inhibitor of Gram +ve bacterium and MTB.54,55 More recently, galanthamine (42),56 originally isolated from Galanthus nivalis, has been approved for the treatment of Alzheimer’s disease. Cebergoline (43),57 a long-lasting dopamine D2 receptor agonist that is used in the treatment of Parkinson’s disease, is another example of a natural product-inspired drug agent. It is an analogue of the naturally occurring ergot alkaloid, a class of biologically active molecules whose membership includes lysergic acid (44).58

4.3. Immunomodulating agents

Several of the most widely employed immunosuppressive agents also arose bearing a natural product connection. The immune suppressive action of the naturally occurring cyclosporin A (45) has been widely credited with the significant increase in the success of organ

58 Aghajanian, G. K.; Bing, Oscar H. L. Clinical Pharmacology and Therapeutics. 1964, 5, 611.
transplantations. More recently, the natural product rapamycin (46) have entered the market as immunosuppressive agent, thereby enhancing the chance for favorable outcomes in organ transplantations (Figure- 9).

![Cyclosporin A (45) and Rapamycin (46)](image)

**Figure-9**

### 4.4. Anticholesteremic agents

It is widely agreed that the statins, inhibitors of the HMG CoA reductase enzyme, are active as anti-cholesteremic agents. They are believed to possess a long-term cardiotoxic benefits. Mavastatin (Compactin, 47), Pravastatin (Pravachol, 48) and Lovastatin (Mevacor, 49) are natural products isolated from *Penicillium brevicompactin*, *Nocardia autotrophica* and *Aspergillus terreus*, respectively. Simvastatin (zocor, 50) is a semisynthetic analogue, closely related to Lovastatin. Atorvastatin (Lipitor, 51) – a mega blockbuster drug belongs to this class of semi synthetic statins (Figure-10).

![Mavastatin (47), Pravastatin (48), Lovastatin (49), Simvastatin (50), Atorvastatin (51)](image)

**Figure-10**

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4.5. Anticancer agents

The natural products reservoir has proven to be a particularly rich source of anticancer lead compounds. A full of 80% of anticancer agents approved between 1981 and 2008 were natural products or natural product-inspired. The major anticancer agents marketed today including vinblastine (10), vincristine (12), and paclitaxel (52) are isolated from natural sources. Taxotere (52), Etoposide (53), teniposide (54), epothilone A & B (55), camptothecin (56), topotecan (57), mitomycin (58) etc. are further examples of application of natural product derivatives to oncology. It is notable that the development in this field via natural products is vibrant (Figure-11).

![Figure-11](image)

4.6. Anti HIV agents

Although significant treatment advances have been made, Acquired Immunodeficiency Syndrome (AIDS), a degenerative disease of the immune and central nervous system continues to be an enormous, incurable health threat. Treatment options have expanded during the past few years, with 19 drugs (all synthetic) now approved for clinical use in the United States. However, many of these drugs cause severe toxicities, including bone marrow suppression, anemia and peripheral neuropathy, and require complicated dosing schedules that are hard to maintain. Their high cost limits their use.

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especially in developing countries where infection is most prevalent. Continuous efforts by NPI (New Partners Initiative, USA) and other laboratories are on to address the issues related to HIV drug development. Screening of plant extracts have resulted in isolation of a large number of compounds with anti-HIV activity 59-66 (Figure-12).

![Chemical Structures](image)

**Figure-12**

### 4.7. Plants as nutraceuticals, preservatives, dyes and colors, flavor and fragrance

In addition to the application of natural products as drugs, for better human health state, natural resources from plants, marine and animal/microorganisms are also contributing significantly towards nutraceuticals as well as coloring agents for food products.

There are some phytochemicals — biologically active natural products as nutrients such as glucosinolates in cruciferous vegetables (cole crops), limonoids in citrus fruits, isoflavones in soy, lignans in flaxseed, lycopene (67) in tomatoes, and catechins (68) in tea. They all have specific actions e.g. diallyl sulfide (69) from garlic which lowers LDL cholesterol, and many of these can be used as antioxidants. They have a positive effect on health. Probably the best known marine nutraceuticals are the omega-3 fatty acids (70) found

71 Sajilata, M. G.; Bajaj, P. R.; Singhal, R. S. *Comprehensive Reviews in Food Science and Food Safety*, 2008, 7, 229.
72 Chan, K. C.; Yin, M. C.; Chao, W-J. *Food and Chemical Toxicology*. 2007, 45, 502.
in fish oils, but are also made available by fermentation technology using microalgae as important sources of products such as polyunsaturated fatty acids, astaxanthin (71), lutein (72), beta carotene (73) (Figure-13).

Many natural dyestuff and stains have been resourced mainly from plants and dominated as sources of natural dyes, producing different colors like red, yellow, blue, black, brown and a combination of these. Natural dyes find use in the coloring to various food products besides coloring of textiles, drugs, cosmetics, etc. owing to their nontoxic effects. In India, there are more than 450 plants known that can yield dyes. Almost all parts of the plants like root, bark, leaf, fruit, wood, seed, flower, etc. produce dyes. It is interesting to note that over 2000 pigments are synthesized by various parts of plants. Natural dyes are environment-friendly, for example, turmeric, the brightest of naturally occurring yellow dyes is a powerful antiseptic which revitalizes the skin, while indigo gives a cooling sensation. Another example is lycopene – a carotenoid pigment responsible for red colour in tomato, watermelon, carrot and other fruits and is also used as a colour ingredient in many food formulations. It has received considerable attention in recent years because of its possible role in the prevention of chronic diseases such as prostate cancer. Epidemiological studies have also shown that increased consumption of lycopene-rich food such as tomatoes is associated with a low risk of cancer. Also it is interesting to note that lycopene is the precursor to bixin and norbixin, pigments from Bixa orellana, commonly used for coloring foodstuff.

Many natural dyes also possess medicinal properties due to their active secondary metabolites and the glorifying examples include tannins from Punica granatum, naphthoquinones such as lawsone from Lawsonia inermis (henna), juglone from walnut and

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73 Chandramouli, K. V. Sources of Natural Dyes in India–A Compendium with Regional Names, PPST Foundation, Chennai, 1995.
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lapachol from alkanet, reported to exhibit antibacterial and antifungal activity. Natural dye powders of *Acacia catechu* (L.f.) Willd, *Kerria lacca*, *Rubia cordifolia* and *Rumex maritimus* have also shown antimicrobial activities. This is clear evidence that some natural dyes by themselves have medicinal properties.

![Chemical Structures](Figure-13)

**4.8. Role of In silico in drug discovery**

It is well established that drug discovery and development is an expensive process due to the high R&D costs and extensive clinical testing with lot of time and resources consuming processes. An alternative approach has been the use of computational techniques in drug discovery and development process. This approach is rapidly gaining popularity and implementation because of several advantages over the wet lab and that include low costs, huge chemical search space, creation and screening, of huge virtual library involving docking (Figure-14) with least animal sacrifice.

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There is an ever growing effort to apply computational power to the combined chemical and biological space in order to expedite and facilitate hit identification, hit-to-lead selection, optimize the absorption, distribution, metabolism, excretion and toxicity profile (ADMET) and avoid safety issues. Introduction of new technologies, such as high-throughput screening (HTS) haven’t resulted in the successful identification of promising drug candidates or reduced the R&D costs. Regulatory agencies as well as pharmaceutical industry are actively involved in development of computational tools that will improve effectiveness and efficiency of drug discovery and development process, decrease use of animals, and increase predictability.

Based on the availability of 3D structure information of the target protein, methods of computer assisted-molecular design is majorly divided into two types i) structure based drug design, ii) ligand based drug design. Docking, Protein homology modeling, and Ligand-receptor binding studies come under structure based drug design where 3D structure of target protein is available. In case of non availability of protein structure Ligand based drug design takes place where methods include QSAR & QSPR (quantitative structure-activity and quantitative structure-property relationships), Pharmacophore modeling, Combinatorial library design, ADME prediction are applied. Researchers can develop the lead molecules by

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carefully studying the 3D-structure of drug targets using x-ray crystallography and/or Nuclear Magnetic Resonance Spectroscopy as well as their interactions.

Successful drugs like Imatinib mesylate (Gleevec), tyrosine kinase inhibitor for chronic myeloid lukaemia, Cimetidine, the prototypical H₂ receptor antagonist have been developed using CADD. Dorzolamide, a carbonic anhydrase inhibitor used to treat glaucoma, Zanamivir an antiviral drug, Donepezil an anticholinesterase inhibitor used in the treatment of Alzheimer’s disease developed using quantitative structural activity relationships studies (QSAR), Indinavir and Nelfinavir, both HIV-1 protease inhibitors. There are so many other CADD success stories of drugs designed and development for example FKP B ligand, K⁺ ion channel blocker, Ca²⁺ antagonist/T-channel blocker, Glyceraldehyde-phosphate DH inhibitors, Thrombin inhibitor, HIV-1 RNA TAR inhibitor, Aldose reductase inhibitors, and DNA gyrase inhibitor, and Aspartic proteases, Renin inhibitors, and Captopril. In nutshell, there is no doubt that in silico studies will benefit future endeavors in the field of drug discovery. This ever increasing
knowledge & continuous advances in technology, paint an extremely bright picture for molecular modeling methodology in future.

5. **Natural products and their derivatives-Future prospect**

Nature has been a source of medicinal products for millennia, and during the past century, many useful drugs have been developed from natural sources, particularly plants. Naturally occurring compounds and their derivatives constitute about one-half of all drugs in current use. They have also provided the molecular template or intellectual stimulus for the synthesis of about half of all synthetically produced medicinal compounds. A statistical analysis of compounds isolated from natural products and those derived by total synthesis employed in drug development has shown that a mere 90,000 known naturally occurring compounds contribute about 40% of total possible new drug molecules, whereas the several millions of synthetic molecules account for the remaining 60%. This remarkable difference in productivity can be attributed to the fact that only a limited number of different molecules are involved in, or have a beneficial effect upon life processes, and that Nature has performed a pre-selection of molecules that influence specific metabolic role in all living things. It is noteworthy that despite the large investment by the pharmaceutical industry in modern-drug-discovery technology, such as combinatorial chemistry and Robotic-based High-Throughput Screening, natural products continue as one of the major sources of new structural entities for drug development. During the investigation of the isolated compounds from natural sources, new insights into the mechanism of drug action have been developed. In this connection, the annals of modern pharmacology have recorded impressive gains from natural products such as heroin, nicotine, acetylcholine, penicillin etc.

Since molecular structure is intricately linked to biological activity, for the medicinal chemist, the natural products represent a treasure trove of possibilities. When the mechanism of action of a compound is unknown, the synthesis and study of carefully designed analogs of the lead compound can be used to fine-tune the drug-molecular target interaction so as to produce the desired biological response. Lastly, lead modification is also

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employed simply to alter the physico-chemical characteristics of a given molecule so that the latter can be amenable to formulation.

Thus keeping in view the above said merits of natural products and their derivatives contribution towards drug discovery, we envisaged to carry out the structural modification of a) Bakuchiol (Chapter-2), b) Piperine (Chapter-3, Section-A), and c) synthesis of structural mimics of piperine (Chapter-3, Section B). All the modified analogs of bakuchiol (Chapter-2) were bio-evaluated for antimicrobial activity especially against oral pathogens. Piperine analogs (Chapter-3, Section-A) and mimics (Chapter-3, Section-B) were bio-evaluated for multidrug resistance efflux pump inhibitors.