Impact of natural products in modern drug development

Sukh Dev
Formerly, INSA Research Professor Indian Institute of Technology Delhi, New Delhi 110 016, India

Usage of natural substances as therapeutic agents in modern medicine has sharply declined from the predominant position held in the early decades of last century, but search for bioactive molecules from nature (plants, animals, microflora) continues to play an important role in fashioning new medicinal agents. With the advent of modern techniques, instrumentation and automation in isolation and structural characterisation, we have on hand an enormous repository of natural compounds. In parallel to this, biology has also made tremendous progress in expanding its frontiers of knowledge. An interplay of these two disciplines constitutes the modern thrust in research in the realm of compounds elaborated by nature. The purpose of this article is to underline how natural products research continues to make significant contributions in the domain of discovery and development of new medicinal products. It is proposed to present the material under several heads, each of which has made natural products research relevant in the search for new and better medication.

Keywords: ACE inhibitors, Anticancer drugs, Antihypertension drugs, Drug discovery, Phytopharmaceuticals

New compounds, new scaffolds

Number of new chemical entities (NCE) emerging as commercial therapeutic agents from Nature has been rather low after the so-called classical period of natural products drug discovery, but natural products continue to provide such compounds as scaffolds to fashion new therapeutic agents. Two examples would suffice to underline this aspect of natural product research.

Antihypertension drugs: Angiotensin-converting enzyme (ACE) inhibitors

Hypertension has been referred to as a ‘silent killer’, as untreated high blood pressure can increase the risk of stroke, heart attack, and kidney damage, hence the need for antihypertension drugs. There are different types of antihypertension drugs, which operate by different mechanisms. It is proposed to highlight one type of these drugs, starting point of which was a natural product, and which made headlines in nineteen eighties.1,2

South American venomous pit viper, Bothrops jararaca, has been known to cause sudden fall in blood pressure in the victim after its bite. Detailed investigations on this snake venom by different groups led to the isolation of several peptides with potent ACE inhibiting activity.1 One of these, a nonapeptide (I) was selected as a model for fashioning synthetic compounds for use as oral antihypertension agents. Captopril (2) was the first such compound to be marketed in 1982 by Squibb (USA). Since then, 13 more drugs fashioned after the same working model have been marketed, the latest two moexipril (Warner-Lambert) and spirapril (Schering-Plough) were launched in 1995(Ref. 3). ACE inhibitors are also used as therapeutic agents in several other medical conditions, essentially originating from hypertension, such as treatment and prevention of heart failure, stroke, and diabetic kidney disease, and currently there is significant research activity in this area.

ACE inhibitors have also been reported from higher plants.4-6 The search for ACE inhibitors led to

![Structure formulae of compounds 1 and 2](image-url)
the discovery of several plants with potent ACE inhibitor activity (Table 1). However, no pure compounds from these plants with specific to the activity have so far been reported. Nonetheless, it may be pointed out that plant *Rauwolfia serpentina* is the source of first important antihypertensive drug. The alkaloid reserpine which mediates this activity through its ganglion-blocking activity, and both ellagic acid and chebulin, constituents of the fruit rind of *Terminalia chebula* have been shown to possess antihypertensive action.

**Anticancer drugs**

It has been estimated that every year, roughly 7 million people die of a variety of cancers worldwide, resulting in search for new and more effective medication. Anticancer drugs is one area of modern therapeutics, which has drawn profoundly on compounds of nature, both for use as such and as platforms for developing more efficacious molecules. Even at present, there is considerable activity in the search for new leads and scaffolds. It is proposed to discuss in the following two such, relatively recent, efforts.

Paclitaxel (3; previously known in the scientific literature as taxol), a diterpenoid, was first isolated as an anticaner compound from the bark of the tree *Taxus brevifolia* Nutt. in 1966, and after several studies and trials, the compound was marketed as an anticancer drug in 1993 by Bristol-Myers Squibb. This lead compound was followed by the marketing of docetaxel (4, Rhone-Poulenc Rorer), a taxane-based compound in 1995. Both the compounds are being used for treating cancers of ovary, breast, and lungs, besides some others malignancies.

Another important contribution in this area involves drugs developed on camptothecin framework. Camptothecin (5), a quinoline alkaloid with anticancer activity, was first isolated from the Chinese tree *Camptotheca acuminata*, but now it is mostly

<table>
<thead>
<tr>
<th>Plant</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cassia occidentalis</em> (leaf)</td>
<td>70</td>
</tr>
<tr>
<td><em>Holarrhena antidysenterica</em> (bark)</td>
<td>84</td>
</tr>
<tr>
<td><em>Leucas aspera</em> (leaf)</td>
<td>96</td>
</tr>
<tr>
<td><em>Litsea glutinosa</em> (bark)</td>
<td>94</td>
</tr>
<tr>
<td><em>Nardostachys jatamansi</em> (rhizome)</td>
<td>89</td>
</tr>
<tr>
<td><em>Phytolacca acinosa</em> (leaf)</td>
<td>96</td>
</tr>
<tr>
<td><em>Rauwolfia serpentina</em> (root)</td>
<td>85</td>
</tr>
<tr>
<td><em>Terminalia chebula</em> (fruit)</td>
<td>82</td>
</tr>
</tbody>
</table>

Fig. 2—Structural formulae of compounds 3 and 4

Fig. 3—Structural formulae of compounds 5, 6, 7 and 8

Irenotecan (6, Yakult Honsha, 1994) is the first camptothecin-based drug targeting solid tumors. Since then, two more drugs of this class have been launched in the market. Topotecan (7, Smith Kline Beecham, 1996), a water soluble derivative of camptothecin with decreased toxicity, is being used as a second-line treatment of ovarian cancer. Beletocan (8, Camtobell, 2004), has been specially evaluated against small cell lung cancer and recurrent ovarian cancer. At least six other compounds of this class are being clinically evaluated 14, 15.

During our evaluation of Indian medicinal plants extracts for various bioactivities, several extracts have shown potent (MIC 2 ppm) anticancer activities against HL-60 (human promyelocytic leukemia cells) cell line 6. However, attention is drawn to the compound morellin (9), first isolated and characterised in India from the seeds of the Indian plant *Garcinia morella* Desr 16. Through the courtesy of Dr. Ramesh Pandey (USA), the compound was evaluated at the US National Institute of Health, and has been found to inhibit several human cancer cell lines, and *in vivo* exhibited anticancer activity against p388 leukemia in CDF1 mice. This compound appears to be a good candidate for further elaboration.

It may be pointed out that significant amount of research effort is being expended to delineate natural molecules, constituents of food materials, which act as cancer preventive agents 7, 17. As an example, it may be mentioned that Indian vegetable karela (*Momordica charantia* Linn., fruit) has potent cancer preventive activity. For example, aqueous extract of its fruit afforded protection from the development of skin tumour in a two-step skin carcinogenesis model in mice 18. A protein MAP30 isolated from the fruit and seeds of this plant, showed antitumour activity against breast cancer MDA-MB-231 *in vitro* and *in vivo* (mice) 19. Two other proteins (α-, and β-momorcharins) obtained from the seeds also possess antitumour activity 20. These proteins have now been found to be ribosome-inactivating proteins, and induce apoptosis and inhibit histone deacetylase-1 selectively in premalignant and malignant prostate cancer cells 21.

**Uncovering different modes of activity**

Another contribution from such studies on natural products has been the opening up of new and novel vistas of their mode of action, which in turn has facilitated mechanism-based drug development.

In the anticancer area, for example, podophyllotoxin-based compounds (10) act by inhibiting topoisomerase II, while camptothecin-derived compounds (*vide supra*) inhibit the enzyme topoisomerase I. Topoisomerases are involved in
DNA replication. On the other hand, both vincristine-type compounds and paclitaxel (3) are antimitotic agents, but whereas vincristine class compounds act by preventing microtubules assembly, Paclitaxel is unique in that it promotes assembly of microtubules and inhibits their disassembly process. Compounds which bind to tubulin, interfere with the assembly of microtubules, resulting in mitotic block, while taxol which enhances the rate of microtubules assembly results in the formation of aberrant microtubule bundles, again leading to the arrest of mitosis. Gambogic acid (11), another important constituent of *Garcinia morella* seeds, has good anticancer profile. Its mode of action appears to be multipronged. It suppresses telomerase activity, inhibits angiogenesis, cancer metastasis, and activates apoptosis.

According to World Heath Organisation (WHO) malaria parasite infect 300 to 500 million people each year and is responsible for death of over a million people every year. After the use of natural product quinine, several synthetic antimalarials have been launched. In the course of time malaria parasite (chiefly) *Plasmodium falciparum* acquired resistance to many of these drugs. So the discovery of a potent antimalarial compound, artemisinin (12) from the Chinese herb, *Artemisia annua* was a welcome break. Artemisinin, and some of its simple derivatives, are active against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* and *P. vivax*, and are equally effective against cerebral malaria. Since these compounds are effective against chloroquine-resistant strains, obviously they operate through a different mechanism. Though, no final picture appears to have emerged, available data is consistent with the drugs interference to the parasite transport proteins, and disruption of parasite mitochondrial function.

As a final example of natural products manifesting different modes of action against a given malady, hypolipidaemic compounds are compared. High plasma cholesterol levels has been recognised as a major contributor for cardiovascular diseases. Currently, statins constitute the important lipid-lowering drugs. The first compound of this class to be marketed was lovastatin (13, Merck, 1987), a metabolite of fungus *Aspergillus terreus*. Since then several other drugs of this class have been marketed. These compounds curtail the biosynthesis of cholesterol by inhibiting the enzyme HMG-CoA reductase, which is crucial for the biosynthesis of mevalonic acid. During the period 1970-80 our work, in collaboration with CDRI, Lucknow, led to the development and marketing of the drug gugulipid, based on guggulsterones (14, 15), constituents of the gum resin from the tree *Commiphora wightii* Bhandari. Gugulipid has a multifocal action. It inhibits cholesterol biosynthesis, mobilises fat from tissues, and

![Structural formula of compounds 12, 13, 14, and 15](image-url)
increases secretion of bile acids\textsuperscript{12}. Since then, guggulsterones have received much international attention, and guggulsterones have been shown to be antagonist of the bile acid receptor (farnesoid X receptor), and this inhibition has been held responsible for their cholesterol-lowering activity.\textsuperscript{31,32}

Multiple activities

Mechanism-based drugs are invariably target-based, and are designed for a particular therapeutic application (one drug, one disease). On the other hand, biologically active natural products, for some unknown reason, quite often exhibit an array of activities. Modern investigators appear to be coming round to view the disease target as enmeshed in the living system, and not in isolation (system biology!), a fact recognised by Ayurveda physicians centuries ago. Possibly, a paradigm shift is in the making, when new drugs, especially those meant for treating cancer, neurological disorders and old-age infirmities, would be broad-based, leading to therapeutic agents with milder, but multifarious related activities.

There is a whole array of natural product molecules with multiple activities, and there is an excellent account of curcumin embracing this subject\textsuperscript{33}. It is not the purpose of this article to give any detailed account of the subject. It would suffice to give two examples of natural compounds first discovered and characterised by us.

From the seeds of bavachi (\textit{Psoralea corylifolia} Linn.) we isolated a meroterpenoid, bakuchiol (16) as a potent antibacterial\textsuperscript{34}. More recently, a group in Japan, showed that bakuchiol has antimicrobial agent against a range of oral microorganisms\textsuperscript{35}. Several workers in different countries while tracking various activities in the extracts of \textit{P. corylifolia} /\textit{P. glandulosa} /\textit{Otholobium pubescens}, ended up with bakuchiol as the active compound that acts as an antioxidant (2002), antiinflammatory (2001), antihyperglycaemic (1999), and inhibitor of DNA polymerase and topoisomerase II (anticancer, 1998)\textsuperscript{7}.

Guggulsterones (14, 15), as already stated above, have been isolated as active hypolipidaemic agents. Guggulsterones have now been shown to activate several other nuclear receptors and induce CYP3A gene expression through the pregnane X receptor\textsuperscript{36}.

Internationally, there is considerable interest in guggulsterones, and as a result several other biological activities have been uncovered, and some of these are anticancer,\textsuperscript{41} antiinflammatory,\textsuperscript{38} antidiabetic,\textsuperscript{39,40} antiarthritic,\textsuperscript{41} cardioprotective\textsuperscript{42} and memory enhancer\textsuperscript{43}.

Incidental scores

Some cases of unintended correlations of known natural products with a biologic system under investigation will be presented in order to highlight the value of exploring natural products diversity \textit{per se}.

Tetrahydrocannabinol (17) was isolated as the psychotropic compound from the Indian plant \textit{Cannabis sativa} Linn. in 1964. This compound and its semisynthetic congeners are used as a probe to characterise two receptors, CB\textsubscript{1} and CB\textsubscript{2}, almost 25-30 years later. These receptors have now been cloned and their natural ligands (endocannabinoids) characterised. The most important CB\textsubscript{1} endocannabinoid is anandamide (18). There is now sufficient evidence implicating endocannabinoids in a wide range of biological functions and their involvement in a growing number of pathological conditions, and presently, there is considerable research activity aimed at exploring these receptors as therapeutic targets\textsuperscript{44,45}.

More evidences are piling up in support of the view that cancers also contain a stem cell, which is responsible for its recurrence. Cancer stem cells have
now been isolated from a variety of tumours, breast, bone, lung and brain cancers. Hence, it is now being considered that medication must destroy the cancer stem cells, if cancer is to be fully eradicated. While looking for small molecules to target the cancer stem cells, parthenolide (19), a sesquiterpenoid first isolated from Chrysanthemum parthenium in 1959, has been found to induce apoptosis in leukemia stem cells. Parthenolide is an inhibitor of NFκB, a protein complex that switches on genes associated with cell growth and proliferation.

One more example should suffice to underline the importance of organic molecules crafted by nature. Studies, on yeast, fruit flies, roundworms, mice, and now on monkeys have highlighted that dietary restriction without malnutrition is one of the most powerful ways to delay ageing. While exploring the possible mechanism of this finding, a group of investigators treated the fruit fly, Drosophila melanogaster, with the immunosuppressant drug rapamycin, and were surprised to note that the effect was similar to what had been observed with caloric restriction. Rapamycin (20) is a macrolide antibiotic, isolated in 1975 from the fermentation broth of the bacterium, Streptomyces hygroscopicus. Rapamycin has been later shown to extend the life span of mice. Target of rapamycin (TOR) protein (kinase), possibly, coordinates several pathways affecting extension of median life span, in various species including humans.

**Phytopharmaceuticals**

Another area where natural products chemistry has played a vital role is the development and marketing of modern herbal drugs, which are produced, standardised, and clinically evaluated just like the conventional molecular drugs.

These preparations which have come to be known as phytomedicines or phytopharmaceuticals, are usually a single plant extract, or an appropriate fraction thereof. This new trend, to a large extent, originated in Europe, especially Germany, where most of the presently leading phytopharmaceuticals were first developed. Most important aspect of these preparations is the need for standardisation and reproducibility. Significant advances in methodology and requisite instrumentation has been taking place to meet these challenges.

**Epilogue**

Natural products chemistry, with its new armamentarium, provides crucial inputs in the development of more effective therapeutic agents, and is a key player in molecular biology. Natural products chemistry engages not only medicine, but also has contributed to agrochemicals, pesticides, and products used in personal sophistication. Above all, it has enriched organic chemistry itself, and on the world scene continues to be an active area of research.

**References**

4. Sukh Dev [Report. submitted during my stint as INSA Research Professor at IIT Delhi (1988-1993), we screened methanol extracts of 200 ayurvedic medicinal plants for a variety of bioactivities in collaboration with NIH (USA), and Takasago (Japan). Several extracts showed potent ACE inhibitory activity (Table1) (Unpublished).


