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Natural product research in the new millennium†

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Abstract

Natural products offer inexhaustible renewable biosources for an array of molecular structures. In addition to bioactive compounds, studies on natural products have led to the understanding of many bioprocesses of great significance in medicine, agriculture, ecology, physiology and provide novel concepts, which open up new vistas for the development of future green technologies. Feasibility of inter-specific gene transfer between organisms provides unlimited scope for future development. There is increasing awareness of potential of nonconventional areas of natural product research such as high-value fine chemicals, advanced starting products for semi-synthesis, plant-based industrial feedstock chemicals, chemical ecology, bioremediation, etc. So far only limited number of flora and organisms have been subjected to some kind of chemical or biological examination; thus vast majority of natural wealth remains unexplored. Studies on marine natural products initiated only recently have yielded molecules with exotic molecular architecture and diverse bioactivity. Well-directed research on natural products will enrich our bioresource base. In the current millennium, India is in a pre-eminent position to contribute towards natural product research with the utilization of its rich knowledge base and biodiversity.

Keywords: Biodiversity, chemodiversity, plant-based industrial chemicals, nonfood uses of plants, oleochemicals, genetic engineering, natural products, designer phytochemicals, biocatalytic synthesis, chemical ecology, bioremediation.

1. Introduction

Advances at the interfaces of chemistry, material sciences, biology, and medicines have triggered intense activity towards the development of novel materials having biotic and abiotic properties. It is the arrangement of atoms within a molecule which imparts properties to it. It is well illustrated by the carbon allotropes. The differences in the properties of graphite (sp^2), diamond (sp^3) or fullerenes (sp^2) are due to different arrangement of carbon atoms. It is more vividly seen in organic molecules. Even slight changes in the spatial arrangements of the atoms can change their bioactivities dramatically as in noninflammatory drug, 2-arylpropionic acid where the activity resides only in the *S*-isomer.[1] Therefore, chemodiversity holds the key for the discovery of bioactive compounds. Materials can be obtained either by synthesis or from natural sources. Recent combinatorial approach to synthesis has greatly increased the scope of synthesis by furnishing a large number of compounds. However, it is no match to the chemodiversity offered by natural products. Nature has the unparalleled capacity to craft molecules with great biological potency. Through natural product research (NPR), in addition to number, rich structural variations can be obtained from a single biological source. During the

†Dedicated to Prof. S. C. Bhattacharyya.

long course of evolution, nature has evolved elegant methods of synthesis, which furnish an array of molecular architectures having varied biological activities.[2]

Varied climatic conditions and diverse topology have contributed greatly towards the biodiversity of India. With mere 2.4% of the global land, India possesses about 8% of total biodiversity. The Western Ghats have been designated as one of the hot spots of global biodiversity.[3] A rich repository of flora with high endemism is found in Himalayas.[4] The immense taxonomic diversity of the country throws a challenge to the Indian chemists and biologists to transform the enormous bioresource into economic wealth as also intellectual property. Food crops, medicines, forest products and fibre are the well-known products from plants. But very little attention has been paid to the potential of noncrop plants, which provide an array of substances of economic value. In addition to conventional products, plants offer many wealth-creating products such as polymer, high-value chemicals (e.g. new generation of drugs, agrochemicals and cosmetics), polymers, resins, rosins, feedstock chemicals, biofuels.

Progress in genetic engineering and biotechnology has added new dimensions to NPR.[5] In fact, the modern natural product research has emerged as a result of amalgamation of the most recent branches of biology, viz. molecular biology, chemical ecology and the most ancient activity in organic chemistry, i.e. phytochemistry.[5] Genetic diversity of natural products offers invaluable materials for genetic engineering (GE). Through well-designed manipulation of genes of natural products, it is possible to engineer the biosynthetic pathways to the desired direction for the production of designer chemicals, oils, lubricants, surface coatings, starches, biopolymer, etc.[6] Further, growing environmental concern on delirious effects of some of the conventional chemical processes call for the development of ecofriendly alternative technologies. Plant-based industries will make increasing contributions in the new millennium.

Advancements in chemical and biological sciences and instrument technology have brought about a revolution in NPR. After an obscurity of several decades, NPR has come to the centre stage of modern scientific endeavors although in India it is yet to get the importance it deserves.[7] Modern NPR is not limited to mere isolation and characterization of compounds but is directed by the newer frontiers dealing with bioorganic chemistry, biotechnology, physiology and ecology. It has become a highly interactive multidisciplinary area of research with contributions from new technologies, highly efficient and fast screening procedures, molecular genetics, structural biology, and synthetic organic chemistry, etc.[8] Well-focused multidisciplinary approach to NPR will open up many new vistas in basic and applied sciences. If the potential of natural products is systematically tapped, India can provide lead to future plant-based industries–phytotechnology.

2. Natural products–Repository of bioactive compounds

Access to molecular diversity is the prime requirement for any discovery programme. It extends from very small molecules to complex ones. Plants and other organisms are the bioreactors of nature. In the form of secondary metabolites they offer unlimited structural variations. They have evolved in response to functional requirements, perhaps due to evolutionary and ecological pressures.[9] Therefore, it is not surprising that they show multifarious bioactivities.

Evaluation of bioactivity by the conventional bioassays has been very time-consuming and major bottleneck in the discovery programmes. Understanding of the fundamental basis of the bioprocesses and availability of various enzymes (through genetic engineering), receptors, cell lines, etc. have contributed to the development of high-throughput test (HTS) which permits fast, high-volume screening using very small quantities.[10] HTS permits quick evaluation of a large number of extracts, natural products and their analogs for specific biological activity. HTS augments the process of bioassay-directed fractionation.

Ethnomedicine will continue to play important role in the future phytotherapy by providing bioactive molecules or important lead compounds. However, it may not be wise to neglect the vast majority of plants, which do not feature in traditional systems of medicine or folklore. With the introduction of HTS, it is possible to screen large numbers of samples including those from random collections. This will increase the resource base and increase the probability of drug discovery. The history of NPR shows that serendipity or chance discoveries have played significant role in the discovery of some of the highly active compounds as exemplified by the discovery of antileukemic drug, vincristine and vinblastine, from the common plant, *Catharanthus roseus*.[11]

Revival of interest and new approach to NPR in recent years has resulted in the discovery of some of the remarkable bioactive compounds (often called *phytotherapeuticals*). Advanced techniques of isolation and characterization of molecules have contributed greatly in bringing NPR to its present status. In the modern NPR, the isolation from the natural products is guided by bioassays. New techniques have made it possible to isolate labile compounds. Structural elucidation by powerful modern nondestructive techniques such as multidimensional NMR spectroscopy, high-resolution mass spectroscopy and X-ray diffraction require only small quantities of samples. Concurrently, biological studies are initiated, mode of action is determined and pharmacophores are identified. The lead molecules allow synthesis of libraries of analogs by combinatorial chemistry for the optimization of activity and other pharmacological parameters.

The modern trends in NPR are illustrated by the following example. Remarkable discovery of taxol from *Taxus brevifolia* triggered intense activity towards the search for alternate sources or compounds with similar bioactivity.[12] Several elegant total syntheses of taxol have been reported but they are not of commercial value and do not supplant the semisynthesis from the more abundantly available 10-deacetylbaccatin from renewable source such as *Taxus baccata* leaves. Within a short time, three different compounds, viz. epothilones (from myxobacteria *Sorangium* sp.), eleutherobin (from soft coral, *Eleutherobia* sp.), discodermolide (from marine sponge) were discovered by bioassay-directed extraction; all the compounds show anticancer activity by an identical mechanism, although they were isolated from different sources and have entirely different chemical structures. They act by the stabilization of tubilin and compete for the same receptor suggesting a common pharmacophore.[13] X-ray studies are being carried out to identify the common pharmacophore so that libraries of analogs can be prepared using combinatorial chemistry.

Introduction of bioassay-directed isolation of active principles has greatly increased our bioresource base and remarkable compounds were isolated from the natural products collected at random. An entirely new class of natural product, namely, OSW-1, a cholestane glycoside, was isolated from an ornamental plant, *Ornithogalum saundersea* (not known to have medicinal properties).[14] It shows anticancer activity by a different mechanism, viz. induction of apoptosis (the programmed cell death). This is the first record of such activity from a cholestane derivative. A well-known triterpenoid, butilinic acid, isolated from a common plant, *Ziziphus mauritiana*, also acts against skin melanoma by inducing apoptosis.[15] The anticancer alkaloid from *Ervatamia microphylla* shows its activity by yet another mechanism, that is by inhibition of the oncogenes such as *ras* or *src*.[16] These examples illustrate that through bioassay-directed NPR, hitherto unknown drug targets could be discovered within a short time. Similarly, several important lead compounds belonging to different classes of natural products which show antiviral (antiHIV) activity, have been isolated. Again, these studies have resulted in the identification of new drug targets such as inhibition of reverse transcriptase or glycosidase or viral protein coat.[17] *The discovery of new targets opens up new fronts for future drug discovery programmes.* Availability of drugs, which act on different targets, is useful for multidrug therapy approach for resistant cases of HIV and other diseases.

The bioassay-directed isolation has led to the discovery of new activities from compounds, which were isolated decades ago. Though ubiquitous, scant attention was paid to the biological activities of flavonoids and related phenolics. Their role in reducing oxidative stress has been well established. Oxidative damages are responsible for many degenerative diseases, such as Alzheimers, diabetes, cardiovascular disorders, cancer as well as radiation sickness. Phytochemicals such as flavonoids and phenolics (*nutraceuticals*) which are present in dietary vegetables and fruits provide natural antioxidants to reduce oxidative stresses. Phenolic constituents of apple have been found to inhibit the proliferation of human cancer cell lines under *in vitro* conditions due to antioxygenic activities of flavonoids.[18]

Much of the phytochemical investigations in the past were centred around the curiosity-driven structure elucidation of compounds or their utility towards human welfare. But the outlook of NPR has undergone changes in the recent times. The role of natural products in the ecodynamics of the organisms is an important area in the emerging discipline of *chemical ecology*. Substantial evidences have accumulated which show that many of the interactions in the biosphere are mediated through the chemicals. During the course of evolution, organisms have acquired effective defense systems, which provide them protection against hostile environment and enemies. The natural defense strategies give cues for the development of entirely new ecofriendly technologies.[19] Organisms produce a stratagem of chemicals, which make them unsuitable for utilization by the predators. Besides the production of toxins, sophisticated defense strategies are provided by the micromolecular constituents, which manifest their effects, by the biochemical intervention of important physiological functions of the predators. It is now well established that secondary metabolites can protect the plants by biotechnical procedures such as suppression of growth, disruption of vital biosynthetic processes or by changing the behavioural pattern of the predators. Occurrence of compounds, which influence the insect life cycle, gives credence to the possible coevolution of plants and insects.[20] For example, highly potent insect growth regulators which occur in many plants can disturb the precise synchronization of insect development by creating imbalance in the normal levels of hormones and derailing the normal metamorphosis by suppressing the ability of insects to reproduce and survive. As an offshoot of basic research on growth regulators, new uses in agriculture and medicine have been found. For example, phytoecdysteroids have been successfully used in sericulture by facilitating the sericulture management programmes.[21]

The range of bioactivities observed in nature goes beyond the imagination of human mind. Even structurally simple molecules such as nitric oxide or ethylene can have profound ecological or physiological significance.[22] Some of the secondary metabolites contribute to the incredible communication systems of nature (biocommunication).[23] Pheromones are the communicatory chemicals, which act at exceedingly low levels and control numerous facets of behaviour of insects.[24] Insect pheromones are relatively simple molecules and are amenable to synthesis. Utility of pheromones in the integrated pest management has been well established. Since they are used in exceedingly small quantities, they do not pose environmental problems. Pheromones and other behaviour-modifying agents will find increasing use in future ecofriendly pest-control measures. The importance of small molecules (including ubiquitous plant volatiles) in ecology has been established. Plant volatiles such as leaf aldehyde can initiate the release of neuropeptides in insects, which in turn initiate the production of pheromones.[25]

A remarkable system of biocommunication has been discovered in tobacco plant. In response to a viral infection, the plant releases volatile air-borne signal, methyl salicylate, which alert the neighbouring healthy plants. The healthy plant converts the methyl salicylate into salicylic acid, which activates the gene PR1 for acquiring resistance, and provides protection to impending attack.[26] Lima beans (*Phaseolus lunatus*) present a more elaborate and subtle interaction of great ecological significance. When attacked by spider mite, it releases volatile alarm substance, which prompts neighbouring plants to activate the gene to produce repellents. But for abiotic stress such as physical injury, compounds with antimicrobial properties are produced.[27] The induction of resistance is likely to find application in future ecofriendly plant-protection measures.

Chemicals play crucial role in the host recognition.[28] Host recognition is of vital importance for the parasites and symbiotic organism. Luteolin, a simple flavone, has been characterized as the gene-inducing substance produced by the host legume for establishing the symbiotic relation with the nitrogen-fixing bacterium, *Rhizobium* sp.

3. Plants as source of feedstock chemicals

Most of the studies on NPR are directed towards discovery of structurally novel compounds or drugs and other bioactive compounds. As mentioned earlier, plants synthesize diverse types of chemical compounds and it is for the chemists to develop methodologies for value addition by appropriate transformations. Advances in plant-breeding techniques, use of fertilizers and agrochemicals such as growth regulators and effective pest-control measures have brought about agricultural revolution in crop production. Future would see a different type of agricultural revolution, which will be based on the wealth-creating potential of noncrop plants. In anticipation of the prospects of the emerging industry, several multinational companies are investing on noncrop plants as source of useful products.

Petroleum, as the main source of fuel and petrochemicals, has certain inherent limitations such as nonbiodegradability, nonrenewability, limited reserve, environmentally hazardous refining processes, etc. To supplement the limited petroleum reserve, some of the oils derived from plants can substitute conventional fuels (biofuels). Through oleochemicals which are present in many noncrop plants, several chemicals of industrial importance can be obtained directly or indirectly.[29] At present, soya, sunflower, palm, rapeseed and groundnut are some of the major sources for oils. Majority of the oil (more than 80%) is used for human consumption, while less than 15% is utilized in industry. But a diverse variety of fatty acid-based products (nonedible oils) occur in plants. A vast majority of plants remains to be explored for potentially useful products. Plant products may find many more nonconventional applications.[30] Some of the higher fatty acids (C_{22}) show excellent properties of high-value lubricants and can substitute presently used whale oil. Plants such as California bay are a rich source of lauric acid, which is in demand by the detergent industry. In addition to direct use, oleochemicals are being converted by simple chemical or biochemical procedures into value-added products such as industrially important feedstock chemicals. Unsaturated fatty acids of many seed oils can be degraded by simple chemical transformation into smaller fragments such as adipic acid, azelaic acid (C_9), brassilic acid (C_{13}). These are important feedstock chemicals. Petroselinic acid, which occurs in abundance in coriander and related plants, can be conveniently degraded into two important feedstock chemicals, viz. adipic acid for polymer industry and lauric acid for the manufacture of soaps and detergents. There are many other nonconventional applications of plant-based products and many more will be added in future such as biofuels, biopolymers, etc.

Some of the natural products are not active themselves but can be useful advanced starting material for the synthesis of high-value products. The steroid industries depend on the phytosteroids obtained from *Dioscorea* sp. and other plants.[11] Baccatin III or 10-deacetylbaccatin, which can be obtained from the leaves of *Taxus baccata* (renewable source), are the starting material for the semisynthesis of taxol.[12]

As an evolutionary requirement, plants growing in soils containing high levels of toxic metals develop ingeneous methods of remediation. Metal detoxification could be due to passive adsorption or fixation by chelation. In response to metal toxification, plants synthesize phytochealatins, which sequester metals to form less toxic complexes. Taking cue from nature, decontamination of waste effluent by using natural products is attracting a lot of attention.[31] Recent researches show that some of the plants and microbes such as *Rhizopus*, sunflower, mustard plants, typha, water hyacinth, *Sesuvium*, banana pith are useful in bioremediation. Success of bioremediation has been demonstrated in pilot-plant scale.[32] Plants and microbes offer many possibilities for bioremediation of low-level high-volume radioactive and toxic wastes.

4. Futuristic technology

Emergence of new areas in biology such as chemical ecology, biotechnology, molecular biology has made an indelible impact on NPR.[5,8] All the biosynthetic processes are under biochemical and genetic control. Geneticists and biotechnologists have just begun to tap the information contained in the genetic library of nature. Restricted occurrence of natural products due to geographical reasons is a serious limitation of NPR. The advent of GE techniques provides alternatives to solve such problems. Microbes have been successfully genetically engineered for the production of high-value, low-volume chemicals which normally occur in plants, microbes or animals such as specialty pharmaceuticals. Now use of plants, instead of microbes, is receiving serious attention for GE. Industrially important products such as designer oils and starches have been obtained from judiciously engineered plants. Plants have the advantage over the microbes since unlike microbes, which require development of elaborate downstream processing, the procedures for the multiplication of plants are already well established or can be developed easily. In fact, a gene for the biosynthesis of lauric acid from California bay tree (which grows in US) has been successfully transferred to rapeseed oil plant, which is extensively cultivated in UK as a crop plant. The GE rapeseed oil plant developed the potentiality of synthesis of lauric acid. Similarly, the genes, which are involved in the biosynthesis of biodegradable biopolymer, biopol (poly-β-hydroxybutyrate) in *Alcagene eutrop*, have been transferred to the rapeseed oil plant; the modified plants produced biopol though in low yields. Even a copolymer could be produced by transferring the genes for appropriate enzymes thus producing a hitherto unknown polymer. It may be noted that as anticipated, multigene transfer has met with less success and more research work is needed to perfect techniques. Many genes, involved in the fatty-acid biosynthesis have been identified, cloned and transferred between plants, microbes and even animals.[33] It can be predicted with confidence that in coming years, it will be possible to engineer most of the plants to produce tailor-made compounds for different chemical and medicinal requirements. ***Demonstration of interchangeability of genetic information between unrelated organisms holds unlimited potential for the development of environmentally sound green chemical technology.***

Through GE, the normal biosynthetic pathways can be diverted into predestined direction. This is illustrated by the demonstration of biocatalytic conversion of glucose to adipic acid, catechol, and hydroquinone by diverting the well-known shikimic acid pathway by ingenious genetic engineering of *E. coli*. Compared to conventional processes, the costs of production of catechol and hydroquinone are quite competitive though that of adipic acid is somewhat higher at present. Attempts are being made to discover better source of glucose.[34] In a novel approach, complex natural products were synthesized in substantial quantities by using the combination of plant biotechnology and synthetic organic transformations.[35] Feasibility of a totally enzyme-based synthesis of a complex natural product, vitamin B_{12}, has been shown by starting from 5-aminolevulinic acid and a combination of 12 enzymes.[36]

5. Conclusions

The extensive biodiversity together with rich traditional knowledge base of India can contribute greatly towards the development of *green technologies* based on plant products. In addition to pharmaceuticals, natural products are receiving increasing attention for their use in futuristic nonconventional areas such as materials science, biotechnology, chemical ecology, production of high-value chemicals, agrotechnology and industrial feedstock chemicals. The interspecific transfer of genes between unrelated organisms provides unlimited scope for future biotechnology. However, overenthusiasm on gene splicing should not ignore the already existing genetic pool. Studies on marine natural products have been initiated only recently. It can be speculated with some confidence that the natural processes will provide lead for the development of novel ecofriendly technologies. Bioremediation will provide methods for decontamination of industrial effluents and radioactive wastes. Valuable endemic plants of our country are finding way out and are commercially exploited after value addition. Therefore, it is not enough to protect our bioassets but efforts should be made for value addition. With the fast disappearance of forests, many of the bioactive compounds hidden in them may be lost to humanity forever. So far, less than 5% of the recorded flora has been investigated; thus vast majority of flora (both terrestrial and marine) remains to be explored. Revitalization of investigations on natural products will expand our resource base and yield rich dividends in terms of furnishing novel molecules, new bioactivities and ecologically acceptable technologies.

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