Research priorities in natural products having CNS effects

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THE history of drugs is intimately woven with plants from the earliest times and even today plant products have extensive use in ethnomedicine, traditional systems of medicine as well as the armamentarium of the modern physician. The recent resurgence of interest in medicinal plants has been partly due to the problems being faced with synthetic drugs, including high cost (over US $200 million)[1] and long time (15–20 years) required for their development, the use of nonrenewable fossil resources as the starting material and environmental-unfriendly technology, as well as their inadequacy in management of certain chronic diseases and toxicity. The natural products in contrast have better patient and public acceptance and tolerance, represent a renewable resource and the technology is comparatively simple and user-friendly. Biodiversity also represents a unique and rich resource of new lead generation[2].

Current status of research on natural products with effects on the central nervous system

International studies

A large number of clinically useful drugs acting on the CNS are plant-derived (morphine, reserpine, ephedrine, atropine, pilocarpine, etc.) as are several drugs of abuse (mescaline, LSD25, cannabis, etc.). Moreover, natural products have initiated new groups of therapeutic agents, the most recent being the psychotropic agents after introduction of reserpine. Valerian is still a useful sedative. In recent years, however, not much work has been carried out in countries other than India on plants having CNS activity. The two notable exceptions are ginseng, which has been widely investigated and used in various countries as an adaptogenic agent and *Ginkgo biloba* alkaloids[3]. Substantial amount of work has also been done on cannabinoids[4].

The national scene

In India, however, many plants have been studied for CNS effects but only few have been evaluated systematically, and the results are summarized in several reviews[5–8]. Hence, only the highlights have been summarized below.

Strictamine, an indole alkaloid isolated from *Alstonia scholaris*, showed MAO inhibitory and antidepressant activity[9]. Alstovenine and venenatine isolated from *A. venenata* also showed significant psychopharmacological properties[10]. The plant is known to be beneficial in the treatment of mental disorders in traditional systems of medicine as well.

The plants showing promising CNS stimulation activity are few and include *Prangos pabularia* and *Conscora decussata*. Osthol isolated from *Prangos pabularia* possessed powerful respiratory stimulant activity[11].

Asarone, isolated from *Acorus calamus*, possessed chlorpromazine-like action[12] but no clinical studies have been undertaken. Jatamansone, isolated from the essential oil of *Nardostachys jatamansi*, also showed tranquilizing activity[13]. The plant is used in the traditional system of medicine. Tranquilizing activity has also been reported in *Paspallum scorbiculatum*[14] and *Celastrus paniculatus*[15]. Other plants showing CNS depressant activity include *Cymopogon citratus*, *Fumaria indica*, *Selinum vaginatum*, *Mesua ferrea* and *Calophyllum inophyllum*[8].

Bacopa monnera exhibits significant nootropic activity and this has been shown to be due to the presence of two saponins, Bacosides A and B[16–18]. Clinical studies have been initiated with the standardized Bacoside mixture. *Celastrus paniculatus* has also been shown to improve learning and memory[19].

Cannabis indica has been studied by the Indian scientists for over 40 years. The plant affects a number of neurotransmitters in the CNS. The abstinence syndrome, tolerance and physical dependence produced by the plant have been studied in a limited way and the most comprehensive study has been done by Chopra *et al.*[20] Earlier too Chopra and Chopra[21] had investigated thoroughly the abuse of opium. The current status of abuse of natural products in the country has been recently reviewed[22].

Many plants have shown analgesic activity. Amongst these, *Embelia ribes*[23], *Randia dumetorum*[24] and *Stepania wighti*[25] need to be mentioned. Promising antipyretic activity has been noticed in several plants, *Wrightia tinctoria* and *Woodfordia floribunda* being quite potent[26]. Important plants having analgesic and anti-inflammatory activities include *Cassia alata*[27],

Curcuma longa[28] and *Desmodium gangeticum*[29]. Out of these, only curcumin from *C. longa* has been studied systematically and is undergoing clinical trials.

Another important area for which plants are being investigated is the adaptogenics. *Withania somnifera, Ocimum sanctum, Cicer arietinum, Panax ginseng* and related species have been shown to possess adaptogenic/ antistress activities in various laboratory models. Kulkarni and Varma[30] have recently reported the ability of a herbal preparation to attenuate the development of tolerance to morphine.

The CDRI programme

The CDRI programme on CNS-active natural products is a part of a comprehensive project on biological evaluation of authenticated samples of natural products. Detailed results have recently been reviewed[8] and experimental methodology published[31]. In a broad-based screening about 3500 plant extracts and about 500 marine organisms have been studied. About 2.6% of the plant extracts showed good CNS depressant activity but no CNS stimulant effect was detected. Among the marine extracts, 2% were CNS depressants but about 6.5% had CNS stimulant activity. These are being systematically followed for isolation and characterization of active constituents and, if indicated, for further development as drugs. The second approach of specialized testing of traditional remedies has been quite rewarding and two of the plants, *Bacopa monniera* and *Curcuma longa*, are under clinical testing. Lead optimization studies resulted in a semisynthetic product, hyatin methiodide, from *Cissampelos pareira*. It exhibited potent neuromuscular blocking activity and reached clinical evaluation[32] but could not be marketed due to development of better synthetic substitutes.

The leads and lacunae of Indian studies

It is evident from this brief review that important leads have been obtained from Indian plants evaluated for CNS activities. Some of the leads in the area of learning and memory, analgesics/antipyretics and adaptogens appear particularly promising. Most of the studies, however, have been of a preliminary nature but few attempts have been made even to isolate and characterize the active constituents. In the majority of the cases nonauthenticated plant material was used and the chemical and biological procedures were often nonstandard. Except for CDRI, no other laboratory has studied marine organisms. The texts of traditional systems of medicine are seldom studied properly for selection of suitable plants. Finally, there seems to be poor awareness of the work done even within the country and the literature is full of repetitive and poorly planned studies.

Priorities and strategies for future research

It is important to pool resources for a coordinated effort on a limited number of plants. The priority areas for new drug development should be memory and learning, psychotropic drugs, adaptogenic agents and plants capable of affecting dependence liability. Any other existing promising leads should be expeditiously exploited.

The choice of natural products is also important. Only authenticated samples should be investigated and it is important to develop centres of systemic botany (and even zoology for marine flora) with good herbaria. For broad-based screening, priority should be given to endemic plants and to threatened species so that the germ plasm could be preserved for active species. The marine flora and fauna are likely to yield novel lead compounds and deserve priority. The plants used in traditional system of medicine should be selected on the basis of published work and authenticated use in these systems.

The tests for biological evaluation need refinement and precision. Facilities for *in vitro*/*ex vivo* binding assays with a battery of neurotransmitter receptors and purified enzyme systems must be set up and leads submitted to CDRI-type *in vivo* screening. There must be associated standardized chemical extraction procedures.

The selection of active plants for preclinical studies must take into consideration the yield of active constituents, availability of the plant, etc. If necessary, synthesis/optimization of activity in semisynthetic compounds may be undertaken. CDRI experience has shown that in selected cases use of properly standardized extracts may give better results and also reduce the cost and requirement of the plant material[33]. This approach is finding greater international acceptance.

The Indian Council of Medical Research has, during the last decade, successfully developed an alternative approach of properly designed clinical trials with drugs used in traditional systems of medicine. The laboratory studies may follow these or be undertaken concurrently. So far, no drug used for treatment of CNS disorders has been selected for such a trial but it appears to be an useful alternative or even a parallel approach.

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Peripheral markers for CNS disease

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GROWING evidence of a biochemical basis for the alterations in nervous activity, including behaviour and mood, has led the neuroscientists to investigate the precise mechanisms of neuropsychiatric disorders. Experimental studies involving animals and in some cases human volunteers have helped in understanding the pathogenesis of a variety of neurological and neuropsychiatric disorders and actions of drugs and chemicals. Delineation of the role of dopamine receptors in Parkinson's disease and the observations that two environmental chemicals, viz. MPTP and manganese, could produce Parkinsonism-like syndrome is one such achievement. Similarly, copper and aluminium have been shown to play a role in Wilson's disease and Alzheimer's disease, respectively. These studies have helped in the development of effective therapeutic drugs and better management of the patients.

Advances in cellular and molecular neurobiology have established that neurotransmitters and their receptors and cellular signalling play a central role in the functioning of the brain. Ever since the understanding that neurotransmitters play a key role in the functioning of the brain[1], neuroscientists have attempted to study them under clinical conditions using body fluids and post-mortem brain samples from disease-affected individuals. The latter studies have provided some useful information. However, the reliability of the data using post-mortem samples is uncertain due to difficulties associated with proper isolation and preservation of the tissue; this could significantly affect