Ethnotherapeutics and modern drug development: The potential of Ayurveda

Sukh Dev

Discovery and development of new therapeutic agents is a continuing process. In spite of the fact that, at present, we have at our command a formidable array of modern drugs\(^1\), the need to discover and invent new agents is genuine and urgent. It has been estimated\(^2\) that satisfactory therapy is available only for about one-third of all presently known human ailments, and several diseases, such as cancer, AIDS, senile dementia, auto-immune diseases, to mention just a few, continue to evade reasonable solution. In addition, in the case of infective diseases, causative organisms continue to develop strains refractory to the medicinal agents, to which they were susceptible earlier. It is being predicted\(^3\) that, due to several other reasons including global warming, infectious diseases may become one of the main scourges of mankind in the near future. Thus, fight against disease must be carried on relentlessly. And, therapeutic agents constitute a very vital ingredient.

Strategies for new drug development

Several strategies have been or are being exploited to discover and invent new therapeutic agents\(^4\). However, basically there are only three approaches: screening, probing human (and mammalian) biochemistry and physiology, and rational drug design. As the techniques and methodologies evolved in each of these areas, they have mutually reinforced each other.

Historically, pharmacological screening of compounds of natural or synthetic origin has been the source of innumerable therapeutic agents. Random screening as a tool in discovering new biologically-active molecules has been most productive in the area of antibiotics\(^5,6\). Chemotaxonomic considerations and target-directed rapid screens\(^7\) played crucial roles in this effort. For a successful outcome the main requirements are access to a large library of compounds/extracts, and well-targeted screens. Recent advances in generation of molecular diversity, in molecular biology and instrumentation have provided a special cutting edge to this approach. Now it is possible to rapidly build up extensive libraries of certain classes of organic compounds by the methods of combinatorial chemistry\(^8-16\). Advances in molecular biology and genetic engineering have enabled biologists to design target-specific screens based on cell-based mechanisms (vide infra)\(^17\). Computerized instrumentation, automation including robotics have vastly speeded up synthesis, structure determination and biological screening. It is now possible to synthesize certain classes of compounds in thousands in a single day, and screen several thousand compounds in a week using just a milligramme or less of each compound!

In the past, probing human/mammalian biochemistry, physiology and causes of certain diseases had led to the discovery of vitamins and certain hormones, which have proved valuable in correcting several deficiency diseases. Steroidal hormones had been the special target for further development\(^18,19\). Prostaglandins, and the related prosta-cyclins and thromboxanes, next, attracted much attention as possible therapeutic agents\(^2,20,21\). With the continuing advances in biology, many physiological cascades and biochemical processes are now fairly well understood at the molecular level. Human body elaborates some 50,000 proteins, comprising hormones, enzymes, immune system proteins, and receptor proteins, and each of these has a distinct function\(^22-24\). In the case of a disease, especially a metabolic one, something had gone wrong with the functioning of these proteins or other non-peptidic bioregulators. Thus, such situations can possibly be corrected by augmenting or by blocking the release of a particular bioregulator or enzyme. This concept, of course, is not new. Insulin was introduced as a therapeutic agent way back in 1923. What made the potential of this knowledge exciting for the pharmaceutical industry\(^25\) was the possible production of these proteins by the methods of modern biotechnology\(^26\). Though this prompted much R&D activity, and several products have since been marketed\(^27\), many pharmaceutical proteins have several shortcomings, including poor oral bioavailability\(^28\). As a consequence, efforts got shifted\(^28-30\) to search for small non-peptidic molecules (ligands, peptidomimetics) which will bind with the receptor.

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proteins (to act as agonists/antagonists/inverse agonists) or inhibit an enzyme or hormone action. It is here where this approach coalesces with the previous one, and the search is now on by screening molecular diversity created by nature or contrived by man. As examples, development of the first β-blocker, as well as the first histamine H₂-receptor antagonist may be cited.

The so-called rational design or the structure-based drug design approach has resulted from the accumulating knowledge of molecular biology. We now have much structural information, mostly from X-ray crystallography and high-field multidimensional NMR spectroscopic studies, on the biopolymers and their complexes with ligands. This has enabled the medicinal chemists to devise small molecules, likely to bind specific receptor proteins or inhibit a particular enzymatic transformation involved in the pathogenesis of disease. There are other biochemical events and entities, such as neurotransmitters, cell replication and protein synthesis (DNA, RNA, transport systems, storage sites, information carriers, etc. which are being targeted in the design of new drugs.

Quantum mechanical considerations, computer-assisted molecular modeling, molecular dynamics, all play a vital role in arriving at structural candidates most likely to have the desired properties. This approach has had some significant successes, and in recent years has been instrumental in the design of drugs effective, though to a limited extent, against AIDS and certain types of cancers.

These approaches, more often than not, result in the discovery of a molecule with desired biological characteristics, the so-called lead molecule, which must then be subjected to structural modification in order to arrive at a molecule with a superior therapeutic index. This process of lead optimization is iterative in nature, and leans heavily on empirical relationships such as QSAR (quantitative structure activity relationship), Hansch analysis, Free-Wilson model, Topliss approach, and so on. As a matter of fact, a practical approach to new drug development is to start with a known drug itself (the so-called me-too approach!) and use the methods of optimization to arrive at a molecule with a better therapeutic profile. This approach has been much exploited by the drug industry, as evidenced from the marketing of second and third generation of certain classes of drugs (vide infra).

All said and done, serendipity continues to play an undefinable, but positive role in drug discovery! There are several examples. However, it is good to remember that Prince Serendip smiles on those who have a sharp, analytical mind and a keen observation faculty!

Higher plants and drug discovery: The role of ethnotherapeutics

Thus, one of the important routes to new drug discovery is accessibility to libraries of compounds and well-directed biological screens, and the game is how to reduce the numbers to be screened before a hit is made. In this context, it will be worthwhile to examine the potential of molecular diversity engineered by nature in the plants. Nature has no parallel in constructing simple or complex molecules in unimaginable modes and shapes, as is evident from our current knowledge of the so-called secondary metabolites.

Classically, higher plants have played a dominant role in the introduction of new therapeutic agents. Even now, contrary to common belief, drugs from higher plants continue to occupy an important niche in modern medicine. On a global basis, at least 130 drugs, all single chemical entities extracted from higher plants, or modified further synthetically, are currently in use, though some of these are now being made synthetically for economic reasons; a listing of 119 such compounds will be found in ref. 48, and some of the newer introductions are covered in this article. Japanese Pharmacopoeia (1896) contains 123 plant drugs, both crude and pure active principles, of which only 29 are used in the Western medicine. In the USA, 25% of all prescriptions dispensed from the community pharmacies during 1959–1980, contained plant extracts or active principles derived from higher plants. Plant-derived drugs constitute important monographs in the German, and Russian Pharmacopoeias. Even now, almost 75–80% of world population depends on crude plant drug preparations to tackle their health problems, though this may be mostly because of economic reasons.

However, the number of new chemical entities (NCEs) emerging as therapeutic agents from higher plants or leads therefrom, has been rather low, after the so-called classical period of plant drug discovery. Thus, the period 1950–70 saw the introduction of approximately 100 basic new drugs in the USA market. However, this list contained no more than five drugs (reserpine, deserpidine, rescinnamine, vinblastine and vincristine) derived from higher plants. Again, during the next twenty year (1971–90) period, over 600 NCEs were launched world-wide, but the number of plant-based drugs, including those fashioned after a plant-based lead structure (teniposide, etoposide, Δ⁴-tetrahydrocannabinol, nablone, lentinam, artemisinin, pluonotol, guggulsterones, ginkgolides) was not even 2% of those. Most recently, the period 1991–95 saw the introduction of around 200 NCEs globally, but the number of these introductions based on higher plants amounted to no more than 2% (paclitaxel, irinotecan, topotecan, gomisin)

There are several reasons for the above situation. Firstly, (most) pharmaceutical companies, the main source of NCEs, have been reluctant to invest in a major way, because of the problems associated with plant collection,
standardization and supply, arising from the fact that, whereas most pharmaceutical houses are located in the economically-developed countries, the biodiversity is available most in the developing countries of the tropics and sub-tropics. Secondly, random screening of plant extracts has not proved economically effective. For example, National Cancer Institute (USA), beginning in 1959 screened over 180,000 plant extracts covering 3500 plant genera during a 20–25 year period, but this did not result in a single drug for the market, though several interesting leads were obtained.\textsuperscript{60,61} Central Drug Research Institute (Lucknow, India) screened approximately 2500 plants for a wide range of pharmacological activities; this programme which scanned some 20 years did not result in a single marketable drug, though many leads were uncovered. A similar effort by CIBA-Geigy Research Centre (Mumbai, India) did not prove productive.\textsuperscript{69} Lastly, but most importantly, with better understanding of etiology of diseases at the molecular level, and further sophistication of structure–activity relationship, it has become a lot easier to generate NCEs, once an innovative breakthrough has been made by someone. This is what has been referred to earlier as the me-too approach. Witness\textsuperscript{4} the second and third generation β-lactams, quinolone antibacterials, β-blockers, inhibitors of angiotensin-converting enzyme (ACE), histamine H\textsubscript{2} receptor antagonists, etc. More specifically, as an example, it may be mentioned that the discovery of ACE inhibitor captopril in 1977 and its subsequent launching as a drug in the market in 1981, spawned no less than fourteen analogues\textsuperscript{49,65} on the drug market between 1983 and 1994. Such proliferation has been the rule in several other therapeutic areas.\textsuperscript{44}

Notwithstanding what has been discussed above, it must be recognized that most of the plant-based drug introductions have been innovative in character, and represent outstanding contributions to therapeutics. For example, introduction of reserpine (1), a constituent of the roots of the Indian plant \textit{Rauwolfia serpentina} Benth., by CIBA (USA) in 1953, was heralded as a revolutionary event in the treatment of hypertension, as it has the twin effect of lowering high blood pressure and acting as a tranquilizer.\textsuperscript{65,66,67} Some of the most important chemotherapeutic agents, currently in use, for the treatment of certain types of cancer are plant-based: vincristine (2, Eli Lilly, 1961) and vinblastine (3, Eli Lilly, 1963), both isolated from \textit{Catharanthus roseus} G. Don., for the treatment of Hodgkin’s disease, lymphosarcoma, and leukemia in children\textsuperscript{50,56,58}, teniposide (4, Sandoz) and etoposide (5), developed from the antineoplastic lignan podophyllotoxin (6), a constituent of \textit{Podophyllum} spp., are currently being used against testicular cancer, small cell lung cancer, and lymphomas\textsuperscript{69–72}; paclitaxel (7, Bristol–Myers Squibb, 1993; previously known in the scientific literature as taxol, hijacked now as a trade mark!), a diterpenoid constituent of several \textit{Taxus} spp., is effective in the treatment of metastatic ovarian cancer, and has potential uses in the treatment of lung cancer, metastatic breast cancer and malignant melanoma\textsuperscript{73–75}; irinotecan (10, Yakult Honsha, 1994), analogue of quinoline alkaloid camptothecin (9), first isolated from the Chinese tree \textit{Camptotheca acuminata}, but now obtained mostly from the Indian tree \textit{Nothapodytes nimmoniana} Mabberley syn. \textit{Mappia foetida} Miers\textsuperscript{76,77} is being used in Japan for the treatment of lung, ovarian, and cervical cancers\textsuperscript{78,79}. As a matter of fact, development of new antineoplastic therapeutic agents based on natural product leads is proving to be a fertile area of activity.\textsuperscript{80,81} Already taxotere (8), a semi-synthetic analogue of taxol is showing much promise in clinical trials.\textsuperscript{81,82} Several derivatives of camptothecin, besides irinotecan already

1. Reserpine

2. Vinblastine (R=Me)

3. Vincristine (R=CHO)
referred to above, are now in clinical phase, and mention may be made of topotecan (11) and 9-aminocamptothecin (12), both of which are showing much promise\textsuperscript{84,85}. Camptothecin itself has potent antineoplastic activity, but has serious side effects, such as causing bleeding in bladder.

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 anti-cancer area, for example, podophyllotoxin-based compounds act by inhibiting topoisomerase II, while camptothecin-derived compounds inhibit the enzyme topoisomerase I; topoisomerases are involved in DNA replication. On the other hand, both vincristine-type compounds and taxol are antimitotic agents, but whereas vincristine class compounds act by preventing microtubules assembly, taxol is unique in that it promotes assembly of microtubules and inhibits their disassembly process\textsuperscript{78,83}. Some of the biologically-active natural products have proved useful as tools in biological and biochemical research, which has a bearing on drug discovery. A good, relatively recent, example would be forskolin (13), a diterpene from the roots of the Indian plant \textit{Coleus forskohlii} Briq. syn., \textit{C. barbatus} Benth., which is being used in purification of adenylate cyclase, and in receptor-binding assays\textsuperscript{86}.

\begin{itemize}
\item \textit{Ethnotherapeutics}
\end{itemize}

From the above, it is clear that higher plants continue to play a useful role in the development of modern
therapeutic agents. It should be possible to optimize this role by diligent planning.

If one looks at how the traditional plant drugs\textsuperscript{47,52} came to be utilized in modern medicine, one will find that invariably, the starting point has been some reference to the use of that plant material as an indigenous cure in a folklore or traditional system of medicine of one culture or another. Table 1 illustrates this point convincingly\textsuperscript{87}.

Table 1. Ethnotherapeutics and traditional modern drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Basis of investigation</th>
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<tbody>
<tr>
<td>Codeine, morphine</td>
<td>Opium, the latex of <strong>Papaver somniferum</strong> used by ancient Sumerians, Egyptians, and Greeks for treatment of headaches, arthritis, and for inducing sleep\textsuperscript{20,123}.</td>
</tr>
<tr>
<td>Atropine, hyoscyamine</td>
<td><em>Atropa belladona</em>, <em>Hyoscyamus niger</em>, etc. were important drugs in Babylonian folklore\textsuperscript{22}.</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Crude drug, <em>Ma-huang</em> (astringent yellow) derived from <em>Ephedra sinica</em> had been used by the Chinese for respiratory ailments since 2700 BC\textsuperscript{22}.</td>
</tr>
<tr>
<td>Quinine, etc.</td>
<td><em>Cinchona</em> spp. were used by Peruvian Indians for the treatment of fevers\textsuperscript{20,122}.</td>
</tr>
<tr>
<td>Emetine</td>
<td>Brazilian Indians and several other South American tribes used roots and rhizomes of <em>Ipecacuanha</em> (<em>Cephaelis</em> spp.) to induce vomiting and cure dysentery\textsuperscript{20,122}.</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Use of <em>Callicium</em> in the treatment of gout has been known in Europe since 78 AD\textsuperscript{21}.</td>
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<tr>
<td>Digoxin, etc.</td>
<td><em>Digitalis</em> leaves were being used in heart therapy in Europe during the 18th century\textsuperscript{21}.</td>
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Results from modern investigations on Chinese medicinal plants strengthen still further the above paradigm that the folklore or classical medicinal plants generate a higher score in our search for molecular therapeutic agents from higher plants. Chinese medicine\textsuperscript{91,92} (Zhong yao in Chinese, Kampo in Japanese) has been practised in China, Japan and other far东方 countries since some 2000 years ago, and its crude drugs are mostly plant-based. For example, Chinese Pharmacopoeia (1990) lists 784 traditional Chinese drugs, of which some 630 are of plant origin\textsuperscript{52,93}. Chinese drugs have been the subject of intense modern scrutiny during the past three decades or so, mostly at the hands of Chinese\textsuperscript{93,99}. Outstanding results have been obtained, essentially confirming many claims of the ancients. A few examples may be cited.

The herb *Artemisia annua* L. has been used traditionally in China for treatment of fevers. It has yielded an effective antimalarial, a sesquiterpene peroxide, artemisinin (qinghaosu, 14). The compound is active against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* and *P. vivax*, and is equally effective against cerebral malaria\textsuperscript{95}. It was introduced world-wide in 1987 (ref. 100). Artemether (15), a simple derivative of artemisinin, has a better clinical profile, and is under active development\textsuperscript{93,101,102}. Gomisin (16), a lignan from the fruits of Chinese medicinal plant *Schizandra chinensis*, has hepatoprotective activity\textsuperscript{93} as revealed from studies carried out in China and Japan, and is being released for treatment of chronic hepatitis\textsuperscript{97}. The Chinese plant *Sophora*...
substrata (roots) has been used in China for treatment of stomach troubles and sophoradin (17), a cholkone, isolated from this has shown significant anti-gastric ulcer activity; a synthetic compound, sofalcone (18) developed after this lead is now in clinical usage98. One more example would suffice. Tea brewed from the leaves of the club moss, Huperzia serrata (Thunb) Trev., has been traditionally used in some parts of China to alleviate memory disorders of the elderly. An alkaloid, named huperzine A (19), has been isolated from this plant, and has been demonstrated to be a powerful acetylcholine esterase (AChE) inhibitor, and is being clinically evaluated for the treatment of Alzheimer disease99.

Plaunotol (20), a diterpene constituent of a Thai medicinal plant plau-noi (Croton slyrantus), has been introduced as a cytoprotective anti-ulcer agent102,103. Modern investigations on folklore medicinal plants of Central Africa104 and Americas105 have lent credence to their folklore usage. One example is cited. Nor-dihydroguaiaretic acid (21), a constituent of the so-called creosote bush (Larrea tridentata) occurring in the South-western US, has been marketed as a treatment for multiple actinic keratoses, a skin affliction, since 1988 (ref. 105).

Ayurveda: Potential and opportunity

At this stage, it appears appropriate to give a brief introduction to Ayurveda for those not familiar with this Indian heritage. The origin of Ayurveda is lost in prehistoric antiquity, but its characteristic concepts appear to have matured between 2500 and 500 BC, in India. The word Ayurveda is derived from Ayus (r), meaning life, and Veda, meaning knowledge, thus, Ayurveda literally means science of life. It is the ancient Indian system of health-care and longevity. Ayurveda takes a
holistic view of man, his health and illness\textsuperscript{106,107}. It aims at positive health, which has been defined as a well-balanced metabolism coupled with a healthy state of being. Disease, according to Ayurveda, can arise from body and/or mind due to external factors or intrinsic causes. Ayurvedic treatment is aimed at the patient as an organic whole, and treatment consists of salubrious use of drugs, diets and certain practices\textsuperscript{108}.

Ayurveda has a vast literature in Sanskrit and various Indian languages, covering all aspects of diseases, therapeutics, and pharmacy; some most important of these are mentioned later. It has evolved its own theoretical base, which is difficult to comprehend in terms of modern scientific concepts, at least at present\textsuperscript{109}. However, in this article we will concern ourselves only with the exploration of its \textit{materia medica}.

Pharmacoeconomics occupies an important place in Ayurveda. Medicinal preparations are invariably complex mixtures, being derived from plant and animal products, as also minerals and metals. Plants form a dominant part of Ayurvedic pharmacopoeia. Earliest references to such plants are to be found in the \textit{Rig Veda} and \textit{Aharva Veda}, dating back to second millennium BC. \textit{Charaka Samhita} (\textasciitilde 900 BC)\textsuperscript{108-112} is the first recorded treatise fully devoted to the concepts and practice of Ayurveda. Its hallmark is \textit{Kayachikitsa} (therapeutics). The work consists of eight sections divided into 150 chapters, and lists 341 plants and plant products for use in medicine. The next landmark in Ayurvedic literature is \textit{Sushruta Samhita} (\textasciitilde 600 BC)\textsuperscript{114-116}, which has special emphasis on surgery. It has six sections covering 186 chapters, and describes 395 medicinal plants, 57 drugs of animal origin, and 64 minerals and metals as therapeutic agents. Sushruta, the father of surgery, lived and practised surgery in Varanasi some 2500 years ago. The next important authority in Ayurveda, after Charaka and Sushruta, was Vaghbatta of Sind, who practised about 7th century AD. His work, \textit{Ashtanga Hridaya}, is considered unrivalled for principles and practice of medicine. \textit{Ashtanga Hridaya} consists of six sections covering 120 chapters, and contains 7444 verses; the entire book is in verse\textsuperscript{111,117}. Charaka, Sushruta, and Vaghbatta are the \textit{Vrihat Traya} (Powerful Triad) of Ayurveda, and their period (900 BC to 1000 AD) is considered as the golden age of Ayurveda. \textit{Madhava Nidana} (\textasciitilde 800 to 900 AD), consisting of 1552 verses in 69 chapters, is the next important milestone. It is the most famous Ayurvedic work on diagnosis of diseases\textsuperscript{115}. Sarangadhara (14th century) systematized Ayurvedic \textit{materia medica}, and his work \textit{Sarangadhara Samhita} consists of three parts, 32 chapters and 2500 verses\textsuperscript{111,118}. The last celebrated writer on Hindu medicine was Bhava Mishra of Magadha, and his treatise \textit{Bhava Prakasha}, written around 1550 is held in high esteem by the modern Ayurvedic practitioner. It has three sections containing 10,831 verses; approximately 470 medicinal plants are described\textsuperscript{116}. Madhava, Sarangadhara and Bhava Mishra have been referred to as the \textit{Laghu Traya} (Junior Three) in the Ayurvedic literature. Besides these monumental treatises, a rather large number (\textasciitilde 70) of \textit{Nighantu Granthis} (Pharmacy Lexicons) were written, mostly between 7th and 16th century\textsuperscript{120,121}. \textit{Raj Nighantu} by Narhari Pandita, and \textit{Madanpala Nighantu} by Madanpala are considered as masterpieces on medicinal plants\textsuperscript{111}. All ancient texts on Ayurveda divide medical knowledge into eight branches (\textit{Ashtanga}). The classifications given by Charaka, Sushruta and Vagabhatta are identical, though differing in order\textsuperscript{115}. Table 2 presents this classification. This treatment is no different from the contemporary approach. Likewise, Ayurvedic description of a disease (Table 3) is also very much like the modern description\textsuperscript{109}. Plant drugs have been classified as per their pharmacological/therapeutical action; Sushruta divides these into 37 categories\textsuperscript{116}, while Charaka places his drugs into 50 groups\textsuperscript{122}. As an illustration, Charaka's classification is shown in Table 4.

From this brief and rather cursory introduction, it must have become obvious that Ayurveda, in its prime time, was a cogent, scientifically organized discipline. This is further borne out by the fact that Ayurvedic texts were much respected in the then contemporary world of neighbouring countries, as evidenced from their translation into Greek (300 BC), Tibetan and Chinese.

<table>
<thead>
<tr>
<th>Table 2. Eight branches of Ayurveda</th>
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<tbody>
<tr>
<td><strong>Sanskrit designation</strong></td>
</tr>
<tr>
<td><strong>Kayachikitsa</strong></td>
</tr>
<tr>
<td><strong>Shalakya Panthra</strong></td>
</tr>
<tr>
<td><strong>Shalyatantra</strong></td>
</tr>
<tr>
<td><strong>Kumararaha</strong></td>
</tr>
<tr>
<td><strong>Agaditana</strong></td>
</tr>
<tr>
<td><strong>Bhavida</strong></td>
</tr>
<tr>
<td><strong>Rasaayana</strong></td>
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<tr>
<td><strong>Vajikarana</strong></td>
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<table>
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<tr>
<th>Table 3. Description of a disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameters</strong></td>
</tr>
<tr>
<td><strong>Sanskrit designation</strong></td>
</tr>
<tr>
<td><strong>Vrakhyasa</strong></td>
</tr>
<tr>
<td><strong>Vraupati</strong></td>
</tr>
<tr>
<td><strong>Nidana</strong></td>
</tr>
<tr>
<td><strong>Purva roup</strong></td>
</tr>
<tr>
<td><strong>Rup</strong></td>
</tr>
<tr>
<td><strong>Sampana</strong></td>
</tr>
<tr>
<td><strong>Sadhya sadhaya</strong></td>
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</tbody>
</table>
Table 4. Classification of plant drugs (Charaka)*

<table>
<thead>
<tr>
<th>No</th>
<th>Sanskrit name</th>
<th>Group</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jivaniya</td>
<td></td>
<td>Promoting longevity</td>
</tr>
<tr>
<td>3</td>
<td>Lekhuniya</td>
<td></td>
<td>Anti-obesity</td>
</tr>
<tr>
<td>6</td>
<td>Dipaniya</td>
<td></td>
<td>Promoter of digestion</td>
</tr>
<tr>
<td>7</td>
<td>Baila</td>
<td></td>
<td>Promoting strength</td>
</tr>
<tr>
<td>8</td>
<td>Varnya</td>
<td></td>
<td>Complexion promoting</td>
</tr>
<tr>
<td>15</td>
<td>Krmighna</td>
<td></td>
<td>Anethimintic</td>
</tr>
<tr>
<td>17</td>
<td>Stanayfana</td>
<td></td>
<td>Galactogogue</td>
</tr>
<tr>
<td>23</td>
<td>Vamannopaga</td>
<td></td>
<td>Emetic</td>
</tr>
<tr>
<td>24</td>
<td>Virechanopaga</td>
<td></td>
<td>Purgative</td>
</tr>
<tr>
<td>35</td>
<td>Mutrairechaniya</td>
<td></td>
<td>Diuretic</td>
</tr>
<tr>
<td>36</td>
<td>Kasahara</td>
<td></td>
<td>Antitussive</td>
</tr>
<tr>
<td>38</td>
<td>Savaahusara</td>
<td></td>
<td>Antiinflammatory</td>
</tr>
<tr>
<td>39</td>
<td>Jvarahara</td>
<td></td>
<td>Febrifuge</td>
</tr>
<tr>
<td>47</td>
<td>Vedanasthapana</td>
<td></td>
<td>Analgesic</td>
</tr>
<tr>
<td>50</td>
<td>Vayahshapana</td>
<td></td>
<td>Anti-aging</td>
</tr>
</tbody>
</table>

*Listing is only partial.
*Numbering as per Charaka.

(300 AD), Persian and Arabic (700 AD), and several languages of other Asian people. In the present-day context, it can be stated that Ayurveda is a very much alive system of medicine widely practised in the Hindustan peninsula and, in recent years has been attracting much attention in the economically developed countries such as (of) Europe, USA, and Japan. The number of registered Ayurvedic practitioners in India are around 250,000 (1988), and if we add to this number countless unregistered and unlisted practitioners the figure may very well come close to 1,000,000. The number of Ayurvedic hospitals and dispensaries (1988) is over thirteen thousand. It has been estimated that a total of some 1000 Ayurvedic remedies, prepared from around 750 plants, are being used at present.

Drug discovery: Potential

With this impressive background, let us now evaluate the potential of Ayurvedic materia medica for leads for modern drug development. With the introduction of western scientific methods in India, many Ayurvedic drugs and other Indian plants with alleged curative properties, soon came under some sort of scrutiny. Such investigations have continued to the present day and the subject matter has been reviewed. There are some success stories, though the number is certainly not commensurate with the long period of research activity. This is undoubtedly due to disorganized, thinly-spread, non-focused effort, and has been commented upon earlier.

Reserpine. The earliest contribution of Ayurveda to modern drug development, which received international attention, and in a way rekindled interest of researchers in possible leads from natural products, is the anti-hypertensive drug reserpine (1), a minor alkaloid of the Ayurvedic drug plant Sarparandha (Rouwolfia serpentina), a brief reference to which has already been made. Roots of this plant are valued in Ayurveda for the treatment of hypertension, insomnia and insanity; as a matter of fact this plant, in local parlance (Hindi-speaking areas), is called pagle ki booti (plant for the insane). As already mentioned, reserpine was introduced in the world market in 1953. Though the starting point for this development was a publication by R. J. Vakil of Mumbai, India, the credit for successful development of the drug from this lead goes entirely to CIBA, Switzerland.

The antihyperlipoproteinemic steroids. The next landmark is the isolation of antihyperlipoproteinemic (hypolipidemic) steroids, Z-guggulsterone (22) and E-guggulsterone (23) from the gum-resin of Commiphora wightii Bhandari syn. C. mukul, Balsamodendron mukul. I would like to deal with this subject in some detail as this is the first example of a dedicated, well-focused effort aimed at development of a modern drug based on Ayurvedic materia medica, and clearly brings out, in a striking manner, the potential and power of this route to modern drug development.

22. Z - Guggulsterone

23. E - Guggulsterone
*Commiphora wightii* is a small tree (Figure 1) belonging to the family Burseraceae. On injury, the plant exudes a yellowish gum-resin, which soon solidifies to an agglomerate of tears or stalactitic pieces (Figure 2) with balsamic odour. This gum-resin, which is called *gugglu* in Sanskrit, is renowned in Ayurveda for treatment of inflammatory disorders, rheumatoid arthritis, lipid disorders, obesity, skin diseases, etc. Some of these claims appeared to be supported by the results of certain pharmacological screening carried out during the period 1960–69 on the crude drug. At the initiative and prompting of (late) C. Dwarkanath, the then Advisor to the Government of India (Ministry of Health) on Ayurveda, a joint programme was organized (1969) to carry out detailed chemical and biological investigations on gugglu with a view to isolating and characterizing the active principle(s). Chemical work was undertaken by my group at the National Chemical Laboratory, Pune, and was later continued at the Mballa Chem Research Centre, Vadodara. All biological work was carried out at the Central Drug Research Institute, Lucknow under the leadership of Nitya Nand and Swaran Nityanand. Though, gugglu has a broad biological activity profile, Dwarkanath stressed the importance of looking at its use in correcting lipid metabolism disorders (*medoroga*), primarily because his group had come across in *Sushruta Samhita* (Sootrasthaanam: 15:32) a *shloka* describing treatment of obesity and other lipid disorders (*medoroga*) with preparations based on gugglu. This *shloka* gives a lucid account of the etiology and pathogenesis of the disease, which is reminiscent of the modern concepts of atherosclerosis and its complications. As a matter of fact, his group had added experimental evidence to show that gugglu has significant hypolipidemic activity. Another practical reason for undertaking work along these lines was the fact that at that time not many drugs with useful hypolipidemic activity were on the market.

Bioassay-guided separation eventually led, in 1971, to the isolation and characterization of two antihyperlipoproteinemic compounds, Z-guggulsterone (22) and E-guggulsterone (23). Both compounds have similar activity which is comparable (Table 5) to that of clofibrate (24), a synthetic hypolipemic drug launched in the market (USA) in 1967. Gugglu gum-resin essentially consists of an ethyl acetate-soluble fraction (~45%) and an insoluble carbohydrate gum (~55%). The latter is toxic to rats and is devoid of any hypolipemic activity. The desired biological activity lies entirely in the ethyl acetate soluble cut. This fraction has been extensively chemically examined, consists of diterpenoids, triterpenoids, steroids, lignans, fatty tetroe esters, etc. A review of this work has been published. The active guggulsterones are present in this fraction to the extent of some 4%. However, a comparison (Table 5) of the activity of this fraction with that of pure

![Figure 1. Commiphora mukul plant. Insert, close-up of the foliage.](image)

![Figure 2. Commiphora mukul resin.](image)
Table 5. A comparison of cholesterol-lowering activity of guggulsterones, cloffibrate and some guggula cuts in rats

<table>
<thead>
<tr>
<th>Product</th>
<th>Normal rats</th>
<th>High fat fed rats</th>
<th>% Inhibition of cholesterol biosynthesis in rat liver homogenate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chol.</td>
<td>TG.</td>
<td>Chol.</td>
</tr>
<tr>
<td>EtOAc soluble (Gugulipid)</td>
<td>34</td>
<td>24</td>
<td>46</td>
</tr>
<tr>
<td>Guggulsterones**</td>
<td>35</td>
<td>28</td>
<td>48</td>
</tr>
<tr>
<td>Total ketones*</td>
<td>30</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Non-ketonic*</td>
<td>15</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>43</td>
<td>30</td>
<td>-</td>
</tr>
</tbody>
</table>

*Data supplied by Nitya Nand.
**Mixture of Z and E-isomers (80:20).
*These represent ketonic and non-ketonic fractions of the neutral cut of the total EtOAc soluble part of the gum-resin (cf. ref. 52).

Guggulsterones showed a vastly disproportionate activity for the total extract, possibly due to synergistic or additive activity of some of the components of the mixture. In view of this, further development of the product (collecting pharmacological, biochemical, toxicological, teratogenic and mutagenic, and clinical data) was carried out on a standardized ethyl acetate extract, code-named gugulipid, containing at least 4% guggulsterones. Gugulipid exhibits a dose-dependent lowering of serum cholesterol and triglycerides in normal and hyperlipidemic rats, rabbits and monkeys. A study of lipoprotein profile in rabbits showed a significant enhancement in the level of the desired high-density lipoproteins, and reduction in the unwanted low-density lipids. It also caused regression of atheromatous lesions induced in rabbits by a fat-rich diet. Gugulipid has a multifocal action: it inhibits cholesterol biosynthesis, mobilizes fat from tissues, and increases secretion of bile acids. Though guggulsterones are pregnane derivatives, they are completely devoid of any estrogenic or antiestrogenic or progesterational activity. Gugulipid was cleared for registration in India in 1986, and the drug has been manufactured and marketed in India since 1987. This material is also being sold in the international market now.

The discovery of antihyperlipoproteinemic guggulsterones in the guggula resin was an event of considerable interest, as these compounds represent a new structural type in hypolipidaemic agents. Consequently, a number of pregnane derivatives were synthesized and evaluated for their hypolipemic activity. One of these (code no. 81/574) was found to be at least as active as guggulsterones, and is currently undergoing clinical trials. Again this has been a joint effort with the Central Drug Research Institute, Lucknow (Nitya Nand).

Additional concordance. As already stated, a fairly large number of Ayurvedic and folklore plants have received some level of scrutiny, and a significant amount of pharmacological, biological and therapeutical data have been generated. Though several of these studies leave much to be desired, a discernible impression, that these investigations have in most cases corroborated some of the ancient claims, clearly emerges. Table 6 summarizes some of the important findings. A few of these call for a brief comment.

Roots of Asparagus racemosus are reputed in Ayurveda as galactogogue, and preparations based on these are used in cases of threatened abortion. Shatavarin-I (25), a component of this plant material, has been shown to produce a specific and competitive block of oxytocin-induced contraction of rat, guinea pig and rabbit uteri in vitro as well as in situ. Galactogogue activity has also received some experimental support.

Modern medicine is quite inadequate for treatment of liver disorders, such as hepatitis (inflammation of the liver), hepatosis (degeneration of the liver parenchyma), chronic hepatitis, and liver cirrhosis. On the other hand, traditional medicine of various countries lays claim to several plants with alleged curative properties. This led to considerable research activity on such plants, including those described in Ayurveda. Of the Ayurvedic plants, modern confirmatory evidence has been obtained for at least three plants: Andrographis paniculata, Picrorrhiza kurroa, Phyllanthus niruri (vide Table 6). The active compounds of A. paniculata and P. kurroa have been identified as andrographolide (26), and picroside (picroside-I, 27; picroside-II, 28) respectively.

Seeds of Butea frondosa constitute an important component of Ayurvedic anthelmintic preparations. Psalasonin (29) has been identified as the active principle.

Psoralea corylifolia seed powder is much valued in Ayurveda for the treatment of vitiligo and other skin diseases. Psoralen (30) has been shown to be the
25. Shatavarin - I

26. Andrographolide

27. Picroside - I (R = cinnamoyl)

28. Picroside - II (R = vanilloyl) (may be C-10 substituted)

29. Palasonin

30. Psoralen

31. Bakuchiol

active principle that stimulates formation of melanin\textsuperscript{165,166}. Bakuchiol (31)\textsuperscript{167-169}, another component, has been shown to possess potent antibacterial activity\textsuperscript{170}, and is effective\textsuperscript{171} against psoriasis, a skin disease.

Though, apparently, the classical Ayurvedic literature does not mention\textsuperscript{172} the use of neem (Azadirachta indica) in treatment of fevers, there is ample folklore literature\textsuperscript{173} on the subject. Recent researches\textsuperscript{174,175} have led to the isolation of gedunin (32) as the antimalarial agent. This tetrarnor-triterpene showed good in vitro activity against certain clones of the causative organism \textit{Plasmodium falciparum}. 
Table 6. Some Ayurvedic crude drugs which have received pharmacological/clinical support for their therapeutic claims

<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Sanskrit name</th>
<th>Active component</th>
<th>Type of activity (Ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acerus calamus</td>
<td>Varcha</td>
<td>?</td>
<td>Tranquilizer (154)</td>
</tr>
<tr>
<td>Adhatoda zeylanica</td>
<td>Vasa</td>
<td>Vasicine</td>
<td>Bronchodilator, oxytocic (224)</td>
</tr>
<tr>
<td>Andrographis paniculata</td>
<td>Bhaunimba</td>
<td>Andrographolide</td>
<td>Hepatoprotector (225-227)</td>
</tr>
<tr>
<td>Asparagus racemosus</td>
<td>Shatavari</td>
<td>Shatavari-I</td>
<td>Anti-aborifacient (228, 229)</td>
</tr>
<tr>
<td>Azadirachta indica</td>
<td>Nimb</td>
<td>Gedunin</td>
<td>Animalarial (172-175)</td>
</tr>
<tr>
<td>Bacopa monnieri</td>
<td>Brahmi</td>
<td>Baccisides</td>
<td>Improves memory (230)</td>
</tr>
<tr>
<td>Bhringhavi diffusa</td>
<td>Pushormana</td>
<td>?</td>
<td>Diuretic, anti-inflammatory (154)</td>
</tr>
<tr>
<td>Butea frondosa</td>
<td>Palasha</td>
<td>Palasonin</td>
<td>Antihelminitic (154, 231)</td>
</tr>
<tr>
<td>Cenella asiatica</td>
<td>Monnokpyrnu</td>
<td>Asantacisides</td>
<td>Skin diseases, psychotropic (154, 232, 233)</td>
</tr>
<tr>
<td>Curcum longa</td>
<td>Haridra</td>
<td>Curcumin</td>
<td>Antiinflammatory (234)</td>
</tr>
<tr>
<td>Holarrhena antidysenterica</td>
<td>Kasua</td>
<td>Conessine</td>
<td>Antidysenteric (170)</td>
</tr>
<tr>
<td>Phyllanthus niruri</td>
<td>Bhoomyaamalakee</td>
<td>?</td>
<td>Hepatoprotector (235-238)</td>
</tr>
<tr>
<td>Pterocarya kurzii</td>
<td>Kaliak</td>
<td>Picrside, kutcoste</td>
<td>Hepatoprotector (239-242)</td>
</tr>
<tr>
<td>Poncidae coelifolia</td>
<td>Bakuchhi</td>
<td>Psoralen, bakuchiol</td>
<td>Antileucoderma, antibacterial (170)</td>
</tr>
<tr>
<td>Swertia chirata</td>
<td>Kairata</td>
<td>?</td>
<td>Febrifuge (243-245)</td>
</tr>
</tbody>
</table>

Thus, modern drug discovery and development is an expensive undertaking but, it is good business. R&D activity is actually the life-blood of pharmaceutical industry. Developing countries like ours are handicapped because of financial constraints. In this article, I have discussed briefly the various routes to drug discovery and development, and have emphasized that Ayurvedic materia medica can be a viable resource for modern drug development. Since this approach drastically cuts down the number of materials to be screened, this along with other points discussed at the end of this article, makes this approach much more attractive from the point of financial inputs. That India, the fountain-head of the Ayurveda, has so far been unable to harness it to its economic advantage is essentially because of lack of well-planned, and clearly-focused effort.

Without any prejudice to other modern strategies, I believe that time is now ripe for countries, such as ours, to explore with all seriousness the crude drugs which have been in use for ages. This is essentially because chemical and biological sciences have reached such a level of development that tracking down of biological activity can be carried out more efficiently and expeditiously. A brief reference to biological developments has already been made. Chemists, also, have at their disposal a range of techniques and methodologies for the isolation, purification, and structure characterization of compounds from plant materials or any other source\(^\text{180}\). It is the interaction of these latest modern techniques and traditional drugs knowledge that confers special appeal and excitement to this approach.

During tenure of my INSA Research Professorship (Dec. 1988–Dec. 1993) at the Department of Chemistry, Indian Institute of Technology, New Delhi, I utilized this period for evaluating over 200 Ayurvedic drugs for a variety of activities\(^\text{181}\) by modern biological methods. Since many of these facilities were not available in the
country, most of the screening work was done by collaboration in Japan and USA. Though results obtained are of a very preliminary nature, I feel it would be worthwhile to highlight some of the findings, as this would demonstrate the power of the modern biological screens.

Learning, memory and cognitive disorders. This area of research was selected because of three main considerations. Firstly, there is a paucity of modern drugs/agents facilitating acquisition, retention, and retrieval of information/knowledge; secondly, with the increasing number of elderly people in the world population, the need for drugs for treatment of cognitive disorders, such as senile dementia, Alzheimer’s disease, have acquired special urgency; and, Ayurveda claims several plants, the so-called Medhya plants, to possess such activities.

The past couple of decades have seen tremendous advances in the area of brain physiology, learning, memory, and various brain disorders, and a host of mechanisms at molecular level have been delineated. Synapses—the junctions of nerve cells representing the basic interactive unit of neuronal circuits—constitute the fundamental systemic relationship within the brain. Understanding how this interactive multitude of neuronal circuity is established initially, and refined continuously throughout life, is fundamental to understanding the molecular basis of learning and memory. At present, an impressive array of chemical entities affecting synapse formation, neuronal differentiation, neurotransmission, nerve growth and repair, and several other functions, are recognized. Some fifty neurotransmitters, belonging to diverse chemical groups, have been identified in the brain. Receptors, which are activated by these chemicals, assume special importance in the present context. Specifically, N-methyl-D-aspartic acid (NMDA) and γ-aminobutyric acid (GABA) receptors have been implicated in learning and memory. It has been further postulated that GABA_A antagonists may enhance memory, while NMDA receptor has the ability to mediate synaptic plasticity. Acetylcholine, the first neurotransmitter to be characterized, has very significant presence in the brain, and recently direct evidence has been obtained that acetylcholine is essential for learning and memory. As a matter of fact, acetylcholine has been a special target for investigations over the past almost two decades, as its deficit, besides other factors, has been held responsible for senile dementia, and other degenerative cognitive disorders, including Alzheimer’s disease. About 5% of the neurons in the hippocampus (part of brain central to learning and memory, and emotions) disappear with each decade after 50 years of age, and the brain tries to compensate for this by further growth of the neurites (neuron axon and dendrites), vital in any case for normal functioning of the brain. Thus, nerve growth factor (NGF) has an important role to play. Several reports have appeared suggesting that angiotensin converting enzyme (ACE) inhibitors (e.g., captopril) may indirectly lead to improved cognitive performance. There are several other factors (e.g., gonadal steroid receptors), which have a bearing on learning and memory, but these will not be discussed, as they are not relevant to the work carried out, and discussed in the sequel.

The above knowledge about neurotransmitters, enzymes, growth factors relevant to memory and learning, and cognitive disorders, is already being harnessed for the discovery and development of suitable therapeutic agents. Major stress has been on acetylcholine. Since with advancing age the number of acetylcholine receptors decline, inhibitors of acetylcholine esterase (AChE), which terminates the action of acetylcholine, have been special targets for development. A brief reference to this was made earlier.

We have looked at some of the Ayurvedic plants reputed as memory enhancers (Medhya) and as anti-aging (Vayuhashapana), by the standard receptor binding, and enzyme inhibition techniques (Table 7), with the specific aim of identifying any leads based on the above considerations. It was gratifying to see several positive results. Shankhapushpi (leaf) is one of the prime medhya plants of Ayurveda; it appears it may be useful for neural regeneration and synaptic plasticity. Jataamansi (rhizome) appears to be an excellent candidate for discovery of an inhibitor of AChE. Our preliminary work shows that the active compound is an alkaloid. Haritaki (fruit) is highly prized in Ayurveda as an anti-aging plant; its extract has displayed several activities. Ashwagandha (Figure 3; root) is another important anti-aging plant. We have investigated this plant in some detail, as its extract showed high affinity for both GABA_A and GABA_B receptors. Receptor-binding-assay guided fractionation of the crude methanol extract resulted in a butanol fraction with retention of GABA_A receptor activity (IC₅₀ ~ 47 μg/ml), and an ‘aqueous fraction’ which retained both GABA_A (IC₅₀ ~ 0.37 μg/ml) and GABA_B (IC₅₀ ~ 15.8 μg/ml) affinity. However, both vaccha and jyotishmati, important Ayurvedic medhya plants, did not show any biological response in these screens. It is quite possible that there are still unknown pathways by which compounds may affect processes of learning and memory, so a negative outcome need not necessarily mean that that particular plant has no scientific basis for its traditional use.

Gastrointestinal disorders, satiety and feeding behaviour. Cholecystokinin (CCK) is a polypeptide hormone widely distributed in the gastrointestinal tract, and nervous system both peripheral and central, and plays a major role in gut function, in the feeding behaviour and digestive process. It also occurs in the brain, where it acts as a neurotransmitter and neuromodulator. CCK
exists as several different molecular species (CCK-58, CCK-39, CCK-33, CCK-8, and CCK-4). The octapeptide CCK-8, for example, predominates in the brain. Also, there are at least two types of CCK receptors\textsuperscript{206-208}.

The past 10–15 years have seen much activity in the area of development of potent and selective CCK agonists and antagonists, as it is believed that these agents may lead to novel therapy for the treatment of disorders such as gastrointestinal disturbances, pancreatitis, gastric and pancreatic carcinomas, obesity, cognition dysfunction, in which CCK has been implicated. Several such molecules are under active development\textsuperscript{208}. Special mention may be made of the so-called satiety agents, fashioned after CCK, to fight obesity\textsuperscript{209}.

In view of the above importance, it appeared worthwhile to evaluate the three components of Triphala (three fruits), an Ayurvedic remedy for treating various gastrointestinal disorders. The three fruits are produce of Terminalia chebula (Sanskrit: Haritaki), Terminalia bellerica (Sanskrit: Bibhitaka), and Emblica officinalis (Sanskrit: Amalaki); haritaki has also been recommended in Ayurveda for treatment of obesity\textsuperscript{210}. The methanol-extracted material from the three fruits was evaluated in vitro by radioligand binding assays (Table 8)\textsuperscript{211}. As is evident from these data, all the three extracts showed good affinity for the CCK receptor, thus offering good opportunity for the isolation and evaluation of new, and possibly clinically useful ligands. We have investigated the extract from T. bellerica (Figure 4) in some detail and have isolated several pure compounds, one of which (code name: B\textsubscript{3}EA-10, m.p. 190–192\degree) showed high affinity (IC\textsubscript{50} \sim 1.8 \mu g/ml).

These investigations in two different areas, though of a very preliminary nature, do serve to highlight the potential of Ayurvedic materia medica for the discovery and development of new molecules for therapeutic use. This approach may have additional advantages (because of traditional usage of the plant material) such as, possibly lesser problems with bioavailability and toxicity, and drug delivery through the oral route.

**Opportunity: Herbal drugs**

Though herbal drugs or phytomedicines, as they are sometimes called, are the very basis of traditional remedies of various cultures, and their tinctures had been inducted in the allopathic medicine in the early decades, they appear to have returned in a more sophisticated form in recent years, in a big way\textsuperscript{212-215}. These drugs are invariably single plant extracts, or fractions thereof, which have been carefully standardized, and their efficacy and safety, for a suggested application, demonstrated. Thus, these drugs, as distinct from well-defined single compound drugs, are complex mixture of many compounds, in which the biologically active compound(s) may not even have been identified. However, in several cases considerable research has also been carried out on their mechanism of action. Except for ginseng, on which most research was done in Japan, most of the other modern herbal drugs have reached the market as

<table>
<thead>
<tr>
<th>Plant (Sanskrit name)</th>
<th>Enzyme inhibition (%)</th>
<th>Receptor binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acorus calamus (Vacchu)</td>
<td>ACE: – AcChE: –</td>
<td>NMDA: – GABA: –</td>
</tr>
<tr>
<td>Bemecata hispida (Koshtomand)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Celastrus paniculatus (Jyotishmait)</td>
<td>Not investigated</td>
<td>–</td>
</tr>
<tr>
<td>Centella asiatica (Mandookpauari)</td>
<td>– AcChE: –</td>
<td>–</td>
</tr>
<tr>
<td>Convulvular macrophyllus (Shankhapushpi)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nardustachys jatamansi</td>
<td>– 90</td>
<td>–</td>
</tr>
<tr>
<td>Ocimum gratissimum (Tulsi)</td>
<td>68 Not investigated</td>
<td>–</td>
</tr>
<tr>
<td>Pluches lanceolata (Rustna)</td>
<td>60 – (B)</td>
<td>99 50</td>
</tr>
<tr>
<td>Terminalia chebula (Haritaki)</td>
<td>82 – (B)</td>
<td>53 53</td>
</tr>
<tr>
<td>Withania somnifera (Ashwagandha)</td>
<td>Not investigated</td>
<td>–</td>
</tr>
</tbody>
</table>

(i) The appropriate plant part, as recommended in Ayurveda, was extracted with methanol by room temperature percolation.

(ii) For biological screening, the methanol-free extract was taken up in aq. DMSO to get 5 \mu g of the material per 1 ml.

Table 7. Modern scientific evaluation of some Ayurvedic Medhya and Vayuahsthapana plants
a result of research conducted in Europe, mainly in Germany, France, and Italy. The European Scientific Co- operative on Phytotherapy (ESCOP) has listed some 150 herbal drugs as beneficial\(^{216}\). In Germany, the Federal Ministry of Health has set up a special Commission (E), which looks after various aspects of herbal drugs\(^{217}\), and these medicines are available as prescription drugs. However, at present, no therapeutic claims are entertained in the US and the same drugs are available there in health food stores as dietary supplements.

Table 9 lists a few of the currently most successful phytomedicines. Beside these, there are several other single-plant drugs, herbal mixtures and teas on the market. It has been estimated that total phytomedicine sales in the countries of European Union, in 1991, were of the order of US $600 crore, of which almost half were sold in Germany alone\(^{215}\). This market is growing at the rate of 15–20% yearly, not only in EU but also in the United States. Of the drugs listed in Table 9, echinacea has the highest market share (US), followed sequentially by garlic (~10%), ginseng (~6%), ginkgo (~4.5%), and saw palmetto (Serenoa repens, ~4.4%); yearly sales of ginkgo products alone in the early 1990s in Europe amounted to US $50 crore\(^{28,219}\). It appears, present global market may be of the order of US $2000 crore. This figure, of course, does not include classical Ayurvedic, Chinese and other traditional herbal preparations share. Their growing popularity has been ascribed to their reasonable standard of effectiveness, minimal side effects, and being economically priced\(^{215}\).

I have given a rather extended introduction to herbal drugs, as I see wide scope for this type of activity for our Ayurvedic and folklore plants. Almost all these modern herbal preparations are based on leads from traditional usage, and areas of application (cf. Table 9) are ‘non-critical’ and ‘non-acute’, often requiring long- term use. The necessary chemical and biological inputs are also limited. This type of development activity clearly falls within the financial means of several of our pharmaceutical companies, and they can reap good dividends. Not much has been done in this area in the country, though herbal (mostly polyherbal) preparations abound in the market. A vast majority of these are non-standardized preparations, with no clinical performance data. Even the recently launched memory enhancer (Memory Plus, Velvette International Pharma Products), developed at CDRI, Lucknow, has become controversial because of lack of any clinical data\(^{217}\). In India the total herbal products market, including sales of crude drugs, has been estimated at Rs 2500 crore, of which ~50% is contributed by Ayurvedic classical preparations and their modernized versions; the export component in this is around 15% (ref. 218). This is a small percentage of the global trade estimated at $2000 crore. Thus, opportunities for developing modern phytomedicines based on leads from Ayurveda, are indeed vast.

**Epilogue**

I have tried to lay bare the opportunities that the Ayurvedic *materia medica* holds for modern drug

<table>
<thead>
<tr>
<th>Plant</th>
<th>Per cent inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Terminalia chebula</em></td>
<td>96</td>
</tr>
<tr>
<td><em>Terminalia bellerica</em></td>
<td>91</td>
</tr>
<tr>
<td><em>Embelica officinalis</em></td>
<td>76</td>
</tr>
</tbody>
</table>

(i) The dried kernel-free fruits were extracted with methanol by room temperature percolation.
(ii) For biological screening, the methanol-free extract was taken up in eq. DMSO to get 5 µg of the material per 1 ml.
Table 9. Herbal medicines popular in Europe and United States

<table>
<thead>
<tr>
<th>Plant (part)</th>
<th>Effective components</th>
<th>Therapeutic claims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panax ginseng</td>
<td>Ginsenosides</td>
<td>Combats feeling of latency and fatigue, adaptogen</td>
</tr>
<tr>
<td>(Root)</td>
<td></td>
<td>Treatment of cerebral and peripheral circulatory disturbances</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Flavonoids and ginkgolides</td>
<td>Immunostimulatory</td>
</tr>
<tr>
<td>(Leaf)</td>
<td></td>
<td>Hypocholesterolemic, hypolipemic</td>
</tr>
<tr>
<td>Echinacea spp.</td>
<td>High mol. wt., polysaccharides; isobutyramides</td>
<td>Treatment of nonmalignant prostate disease</td>
</tr>
<tr>
<td>(Root, aerial part)</td>
<td></td>
<td>Treatment of mild depression, nervousness</td>
</tr>
<tr>
<td>Allium sativum</td>
<td>Alliin and other related compounds</td>
<td></td>
</tr>
<tr>
<td>(Bulb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serenoa repens</td>
<td>Polysaccharides</td>
<td></td>
</tr>
<tr>
<td>(Fruit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypericum perforatum (Leaf, flower)</td>
<td>Flavonoids (?)</td>
<td>Treatment of nonmalignant prostate disease</td>
</tr>
<tr>
<td>Valeriana officinalis (Root)</td>
<td>Sesquiterpene acids; valepotriates</td>
<td></td>
</tr>
<tr>
<td>Flower pollen</td>
<td>?</td>
<td>Benign prostatic hyperplasia</td>
</tr>
</tbody>
</table>

References and notes

1. Sukh Dev, Proc. Indian Natl. Sci. Acad., 1988, 54A, 12. Modern drug may be defined as a clinically efficacious chemical entity or mixture, of synthetic or natural origin, administered as such or admixed with other entities or vehicles and being produced in a reproducible form under good analytical control. The term clinically efficacious is meant to convey that the said product has undergone pharmacological, toxicological and clinical screening as per accepted parameters of modern medical sciences.


22. Anon., Chemtech, 1988, 18, 84.


42. Rawls, R., C&EN, 1996, April 8, 37.
51. This figure has been extrapolated from the data available for the period 1983-91: Annu. Rep. Med. Chem., 1992, 27, 357.
55. Both guggulsterones and ginkgolides are currently being marketed as standardized extracts.
61. However, it must be pointed out that two compounds (taxol, camptothecin) discovered during these investigations have acquired much importance in recent years as anti-cancer agents.
64. An innovative therapeutic agent has been defined as a chemical whose use in a given indication had little or no precedent before its introduction and whose use also represents a very significant improvement over, or a very significant supplement to, available drugs.
71. Ref. 50, pp. 610, 1440.
83. Ref. 41, p. 133.
85. Compounds which bind to tubulin, interfere with the assembly of microtubules, resulting in mitotic block, which taxol which enhances the rate of microtubules assembly results in the formation of aberrant microtubule bundles, again leading to the arrest of mitosis (Ref. 73, p. 307).
87. Also see: a. Kupchan, S. M., in Drug Discovery, American Chemical

88. Mukerji, B., Medical Lectures II, Indian National Science Academy, New Delhi, pp. 973.


95. Huang, L., in Natural Products and Drug Research (eds Krogsugard-Larsen, Christensen, S. B. and Kofod, H.), Munksgaard, Copenhagen, 1984, p. 94.


103. Ref. 100, p. 340.


106. 'The understanding of a totality of an entity does not arise from a fragmentary knowledge of it' (Charaka Samhita, VI, 4.5). This is now being considered in allopathic medicine! See e.g., Pietroni, P. C., J. R. Soc. Med., 1978, 80, 337.


109. Charaka Samhita is, in fact, an edited and enlarged version of an older treatise (Tantra) by Agnivesha, which was based on discussions and proceedings of a series of meetings and symposia, organized by his preceptor Atreyu Punarvasu. Charaka Samhita was redacted and enlarged later by other scholars, most important amongst these, being Dhritahabu.


115. Majumdar, R. C., in A Concise History of Science in India (eds Bose, D. M., Sen, S. N. and Subbarayanapa, B. V.), Indian National Science Academy, New Delhi, 1971, p. 222.


118. Surangadharasamhita (edited and published by Dikshit, Y. G.), Pune, 1908.


121. Ref. 115, p. 264.

122. See e.g., Ray, P. and Gupta, H. N., Caraka Samhita, National Institute of Sciences of India, New Delhi, 1965, p. 27.


127. See Chopra, D., cited in ref. 105.


129. Sharma, S., Reader's Digest (India), 1978, (November/December), 255.


144. It is remarkable that in Ayurvedic pharmacy practice, raw guggulu is first purified (shuddhan) before its incorporation into any for-
null
GENERAL ARTICLE

Evaluation Unit Programme (Boca Raton, Florida, June, 1993) and at Annual Meeting of American Society of Pharmacognosy (San Diego, California, July, 1993).


216. Phytomedicine, 1994, 1, 173.


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