NATURAL PRODUCTS IN MEDICINE—PRESENT STATUS AND FUTURE PROSPECTS*

SUKH DEV
Malti-Chem Research Centre, Nandesari, Vadodara 391 340, India.

FROM his first awakening man has sought to fight and control diseases, and turned to Nature for inspiration and guidance. During thousands of years of early human existence, many natural materials, by instinct or intuition or trial and error got in use for combating human ailments. Thus, the classical medical systems, such as Ayurveda of India and the folk-lore of various countries, lean heavily on natural products. Natural products have been derived from higher plants, microbes or animals, and these can be of either terrestrial or marine or aquatic in origin. The medicinal preparations based on these raw materials were in the form of crude drug such as a dried herb or an extract thereof and were invariably derived from a mixture of several materials. With the advent of European scientific methods, many of these reputed medi cinal plants came under chemical scrutiny, leading to the isolation of active principles. Beginning with A.D. 1800 there was continuous activity in this area and many of the well-known medicinal plants were chemically analysed and their active principles characterised. Soon after their isolation and characterisation, these compounds either in pure state or in the form of well-characterised extracts, became part of pharmacopoeias of several countries.

While this phase of modern medicine was developing, chemists and pharmacologists were busy in synthesising and evaluating new molecules. However, the biggest impetus for the synthesis of drugs came by the close of nineteenth century when Paul Ehrlich propounded his concept of chemotherapy. Ever since there has been more and more activity in this area and more and more synthetic drugs came to be utilized for treatment of human and veterinary diseases. At present it is generally thought that natural products have lost much of their importance. This, in fact, is not true. An analysis of prescriptions dispensed from community pharmacies in USA was carried out[1] in 1973 and this showed that as many as 41% of the prescriptions contained one or more products of natural origin as the therapeutic agent. The total value of these prescriptions was of the order of Rs. 3000 crores. Of these prescriptions, 25% were derived from higher plants, some 13% represented metabolites of microbes and about 7% were of animal origin. Another recent (1978) reference[2] mentions that 25% of the 200 most frequently prescribed drugs in the USA, were of natural provenance. The situation would appear to be similar for many other countries including India, and as a matter of fact, this figure may be even higher for Soviet Union, Germany and Italy.

More than 75 pure compounds derived from higher plants find their place in modern medicine and some of the traditional ones are shown[1] in table 1. However, it may be noted that ψ-ephedrine, ephedrine, emetine, caffeine, theobromine, theophylline and papaverine are now mostly produced synthetically, for economic reasons. This brief introduction should serve to drive home the importance of natural products in the present-day medicine.

NEWER DEVELOPMENTS AND STRATEGIES FOR DRUG DISCOVERY FROM NATURAL SOURCES

However, most of the drugs discussed so far, were discovered and introduced in modern pharmacopoeias during 1850–1950. Beginning with 1950 science has made rapid, often overwhelming strides along all its facets and medicine has been no exception. Breakthroughs in a discipline are often the results of outstanding progress in related disciplines. Advances in chemistry, physiology, biology and physics, coupled with development of technology for isolation, analysis, characterisation and structure recognition have

* Based on a lecture delivered at the International Seminar on Medicinal Plants, Phytochemicals and Bulk Drugs, held in New Delhi on March 23, 1983.

TABLE 1.

Important traditional active plant principles

No.	Drug	Plant source	% of total R_{xs}
1.	Codeine	*Papaver somniferum*	2.03
2.	Atropine	*Hyoscyamus muticus*	1.50
3.	ψ-Ephedrine*	*Ephedra* spp.	0.90
4.	Ephedrine*	*Ephedra* spp.	0.77
5.	Hyoscyamine	*Hyoscyamus muticus*	1.00
6.	Digoxin	*Digitalis lanata*	0.73
7.	Hyoscine	*Datura metel*	0.66
8.	Digitoxin	*Digitalis purpurea*	0.33
9.	Pilocarpine	*Pilocarpus jaborandi*	0.26
10.	Quinidine	*Cinchona* spp.	0.18
11.	Quinine	*Cinchona* spp.	–
12.	Emetine*	*Cephaelis* spp.	–
13.	Caffeine*	*Thea sinensis*	–
14.	Theobromine*	*Theobromo cacao*	–
15.	Theophylline*	*Coffea arabica*	–
16.	Papaverine*	*Papaver* spp.	–
17.	Colchicine	*Colchisum autumnale*	–

*Now mostly produced synthetically

led to great advances in drug development. The contributions of natural products to medicine during the period after 1950 have been outstanding and these will be briefly reviewed. Chemical compounds have been obtained from higher plants, microbes and animals, but we shall restrict our discussion to products derived from plants and animals, though, microbial metabolites[3,4] constitute a vast field, the subject is not directly relevant to the present theme.

A chemical entity derived from nature may be useful as a drug by itself or it might serve as a raw material, best suited for chemical processing into a drug. Or, it may be suitably derivatised to optimise a particular biological activity leading to what are called semisynthetic drugs. Alternatively, it may serve as a model for development of a totally synthetic drug. Since, it is not proposed to take up natural products as raw materials for drugs, it would suffice to mention that steroidal hormones provide an excellent example, as they are almost entirely produced[5,6] from other steroids such as diosgenin, stigmasterol or sitosterol, which are not drugs *per se*. It is proposed to discuss briefly the remaining aspects.

How does one go about discovering a natural product for use in medicine? Various strategies have proved useful and these may be classified into the following three categories:

(1) Recognition of hormones, bio-regulators, enzymes and enzyme inhibitors from a study of mammalian (preferably human) biochemistry and physiology.
(2) Random search and chemotaxonomic considerations.
(3) Ethnotherapeutics: folklore and traditional systems of medicine.

It will be worthwhile to discuss newer developments and future potential in terms of these strategies.

Mammalian Chemistry and Drug Development

This has been a very potent source of drug development. Important, well-known examples are insulin, thyroxine, sex hormones, adrenocortical hormones, oxytocin, many of which were introduced in clinical usage between 1950–1960.

Special attention may be drawn to the steroidal sex and adrenocortical hormones[7], the study of which dominated drug development from natural sources during the 1950–1965 period, when several semisynthetic analogues[8] with superior therapeutic activity were discovered and launched.

Beginning around 1960, a great deal of attention and effort began to be expended on other bioregulators of importance to mammlian physiology. This phase overlapped an era when steroid research appeared to have reached a point of low returns, and these areas appeared to be promising. These investigations resulted in the recognition of several polypeptides as important hormones, and a number of C_{20} lipid acids, designated as prostaglandins, as important bioregulators.

Peptide hormones[9] are released by thymus, hypothalamus, pituitary, thyroid, pancreas and even by gastrointestinal mucosa. The technique of radioimmunoassay[10] played an important role in these investigations. Many of these results have clinical applications. As an example, it may be mentioned that human calcitonin, a hormone originating from the thyroid gland, is now being manufacturod by a synthetic process[11] and is used in the clinical treatment of Paget's disease. While on the subject, it should be pointed out that at least some of the these hormones are candidates for production by what has come to be known as genetic engineering[12]. This powerful technology is being vigorously refined and is considered to have extensive scope for the production of medicinals for human and veterinary use[13] (and even in plant cytogenetics which have a direct bearing on the production of phytochemicals). The first drug produced by genetic engineering is human insulin and was released in UK in 1981 for clinical application, under the trade name Humulin (Eli Lilly)[14].

As already mentioned, prostaglandins[15,16] represent another important field arising from the study of animal chemistry. It was von Euler of Karolinska Institute, Sweden, who following earlier observations, found that human seminal plasma stimulated a variety of smooth muscles. He recognised the presence of an active principle and named it prostaglandin (1935) thinking that it is being biosynthesis by the prostate gland. Though this belief has since been proved to be erroneous, the term prostaglandin has been retained. Prostaglandin research suffered a setback because of the Second World War, but the thread was picked up by Bergstrom after the War, who showed (1949) that more than one prostaglandin are present and he succeeded in the isolation and structure elucidation of a number of prostaglandins during the period 1950–62. It was thus recognised that prostaglandins are based on the C_{20} fatty acid arachidonic acid (figure 1), and that prostaglandins are ubiquitous in mammalian tissues. If was further shown that prostaglandins exhibit a diverse spectrum of biological activity and that also at exceedingly low concentrations. Thus, some prostaglandins contract, others relax smooth muscle, some promote leuckocyte migration, some regulate gastric secretions, some promote while others prevent platelet aggregation. Further studies led to the discovery of other closely-related compounds which are also biologically active at very low concentrations. These are also shown in figure 1. Thus, prostacyclin

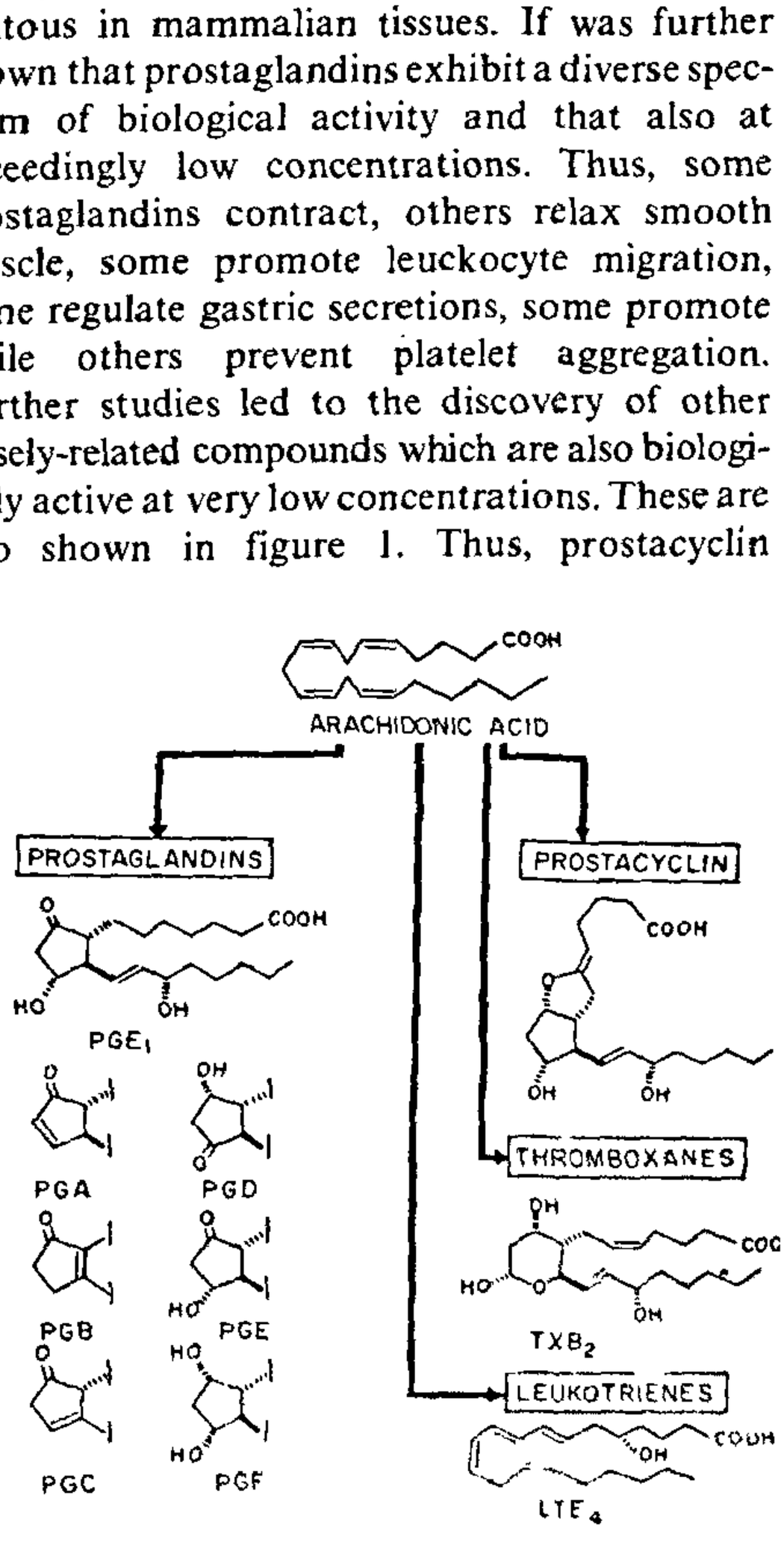
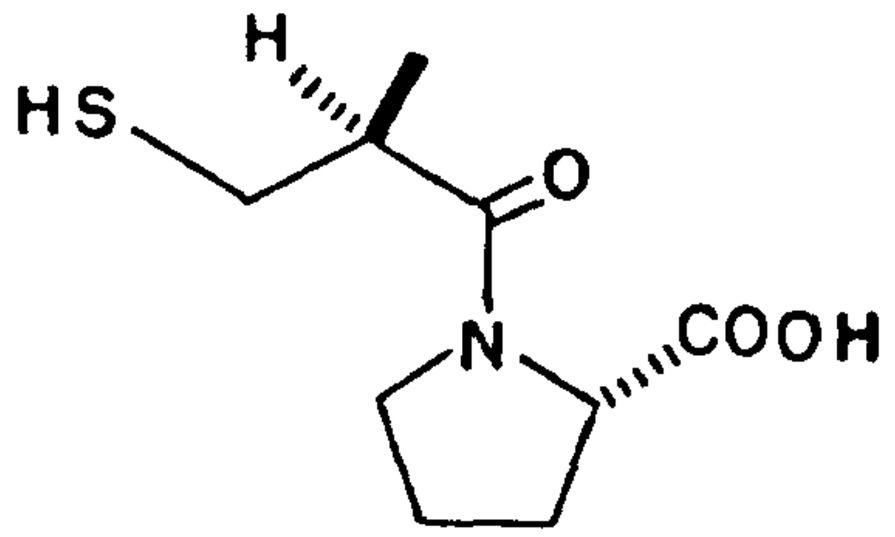


Figure 1. Eicosanoids.

(PGI_2)[17], which has pronounced antihypertensive and platelet aggregation-inhibiting properties, thromboxanes[16] (*e.g.* thromboxane A_2 is a powerful prostacyclin antagonist), and leukotrienes[18] important mediators in asthma—are all closely related to prostaglandins. All these compounds arise from enzymic oxidation of arachidonic acid and this group has come to be known as eicosanoids[16].

Prostaglandins and related compounds have considerable potential for clinical utility in reproductive, respiratory, gastrointestinal, and cardiovascular-renal systems. As a matter of fact, a number of prostaglandins and their analogues have been released for clinical and veterinary use[16] and some of these are shown in figure 2.

While on the subject of drugs based on human and animal secretions, mention must be made of a potent, orally effective hypotensive drug, Captopril (1; 1981, Squibb)[19], a synthetic peptide, patterned after the active principle, a nonapeptide, in the venom of South American pit viper, *Bothrops fararaca*.



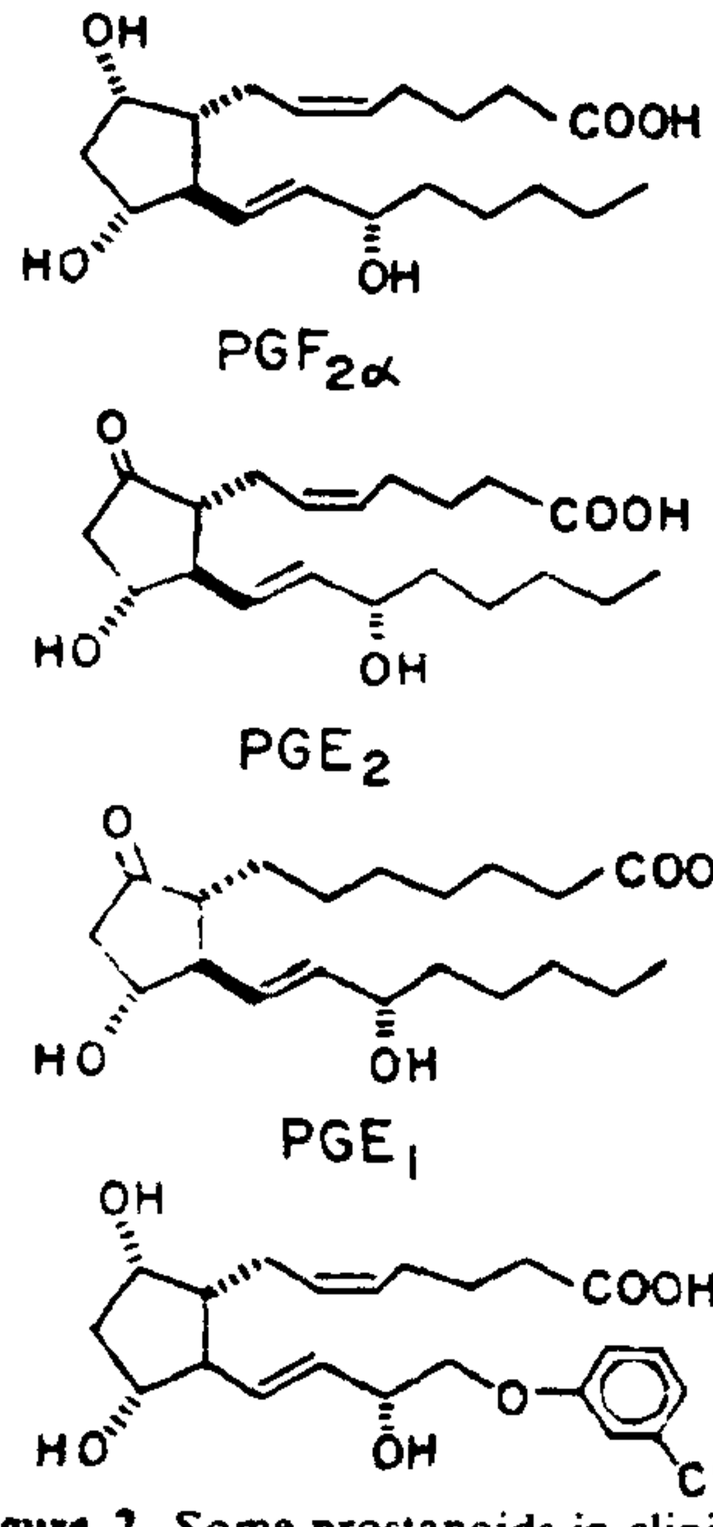
Captopril

(1)

Random Search and Ethnotherapeutics

Random search (and chemotaxonomic considerations), and examination of ethnotherapeutics consitute important strategies in search of drugs from higher plants, and marine flora and fauna.

Research aimed at discovering new drugs from higher plants has been rather erratic during the period 1950–80, mainly as pharmaceutical indus-



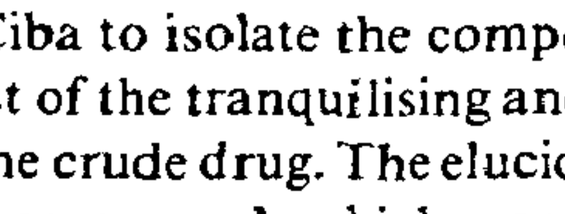
	DINOPROST (1973)	Upjohn	Induce labor, abortion and menstruation
	DINOROSTONE (1977)	Upjohn	Induce labor, abortion, cervical softening; treat stress ulcers
	ALPROSTADIL (1982)	Upjohn	Treat peripheral vascular disease. preinfarctional angina & stroke
	CLOPROSTENOL (1975)	ICI	Synchronize estrus in cows

Figure 2. Some prostanoids in clinical/veterinary use.

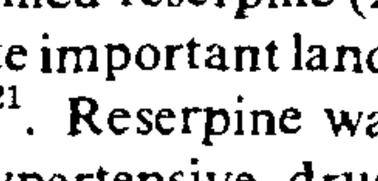
try has been reluctant to invest in a major way, because of problems associated with plant collection, standardisation and supply. Thus though during the period 1950-1970, approximately one hundred basic new drugs were introduced[20] in the USA, contribution from higher plants was a mere five drugs (reserpine, deserpidine, rescinnamine, vinblastine and vincristine). However, reserpine, vinblastine and vincristine represent outstanding contributions to drug development.

Rauwolfia serpentina (Sanskrit, *Sarpgandha*) is a well-recognised drug for the treatment of hypertension, insomnia and insanity, in the Ayurvedic system of medicine. Though, earlier investigations, with a view to isolating the active constituent proved futile, the crude drug came into focus again as a result of a publication (1949) on its antihypertensive activity by Vakil. Systematic separation, aided by biological assay, enabled Schlittler, Muller and Bein (1952) at Ciba to isolate the compound responsible for most of the tranquilising and hypotensive effects of the crude drug. The elucidation of structure of this compound, which was named reserpine (2) and its total synthesis constitute important landmarks, in alkaloid chemistry[21]. Reserpine was first introduced as an antihypertensive drug, under the trade name Serpasil[22] in U.S. by Ciba in 1953. A few years later (1956) rescinnamine (3) which is 3,4,5-trimethoxycinnamic ester of methyl reserpate and is present in *Rauwolfia* plants but is more easily obtained by a partial synthesis, was introduced in U.S. by Pfizer, as an antihypertensive drug[22]. This was followed by another closely related compound, deserpidine (4; Abbott; 1957, U.S.), a component of *Rauwolfia canescens* again as another hypotensive agent[22].

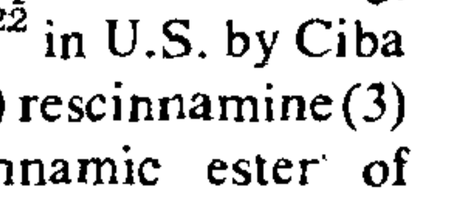
This success with *Rauwolfia* alkaloids led to a virtual renaissence in plant drug research, but with limited success and by the end of 1965 most pharmaceutical houses had abandoned this area of drug development. However; this period saw the emergence[22] of two dimeric alkaloids, vinblastine (5) and vincristine (6), as drugs for the treatment of Hodgkin's disease, lymphosarcoma and leukaemia in children. Work on periwinkle plant, *Catharanthus roseus*, (L) G. Don was independently taken up in two different laboratories for its alleged hypoglycemic activity as per Jamaican folklore. Though one of the groups could substantiate hypoglycemic activity, the



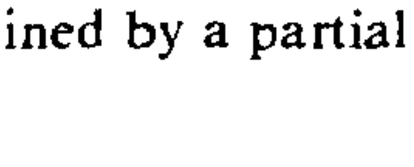
Reserpine (2) : R = OMe

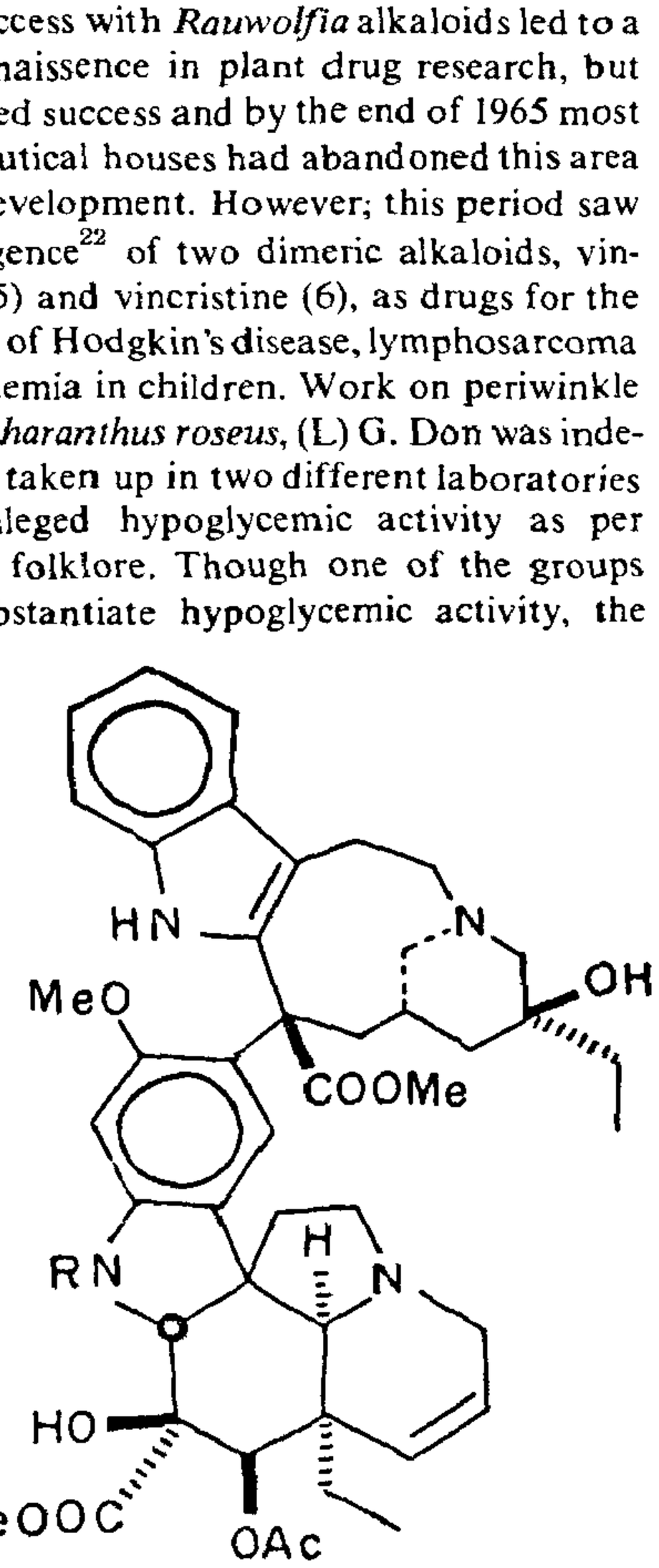


Rescinnamine (3) : R = OMe



Deserpidine (4) R = H



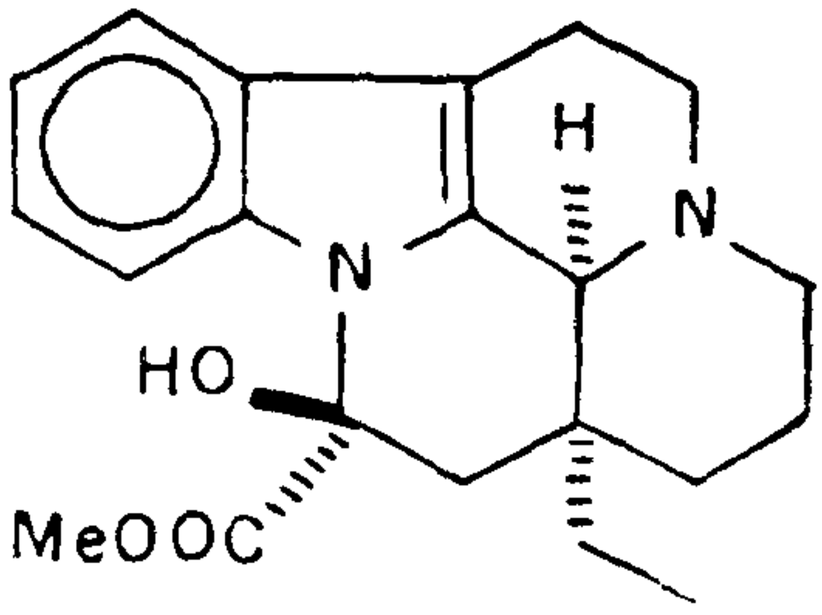


Vinblastine (5) : R = Me

Vincristine (6) : R = CHO

Canadian group of Noble, Beer and Cutts succeeded in isolating vinblastine, while Eli Lilly group which included Johnson, Svoboda and others could isolate vinblastine and vincristine and two other active dimeric alkaloids. These alkaloids are present in exceedingly low concentrations, in a complex mixture of over 50 alkaloids, and their isolation was made possible only as separation was systematically led by appropriate pharmacological assays[21,23]. Vinblastine was introduced as a drug (Velban, Eli Lilly) in 1961, and vincristine (Oncovin, Eli Lilly) in 1963[22]. A semisynthetic derivative vindesine, which is 4-deacetylvinblastine-3-carboxamide, has been recently (1980) marketed as an antitumor drug in Europe, under the trade name Eldisine, by Eli Lilly[24].

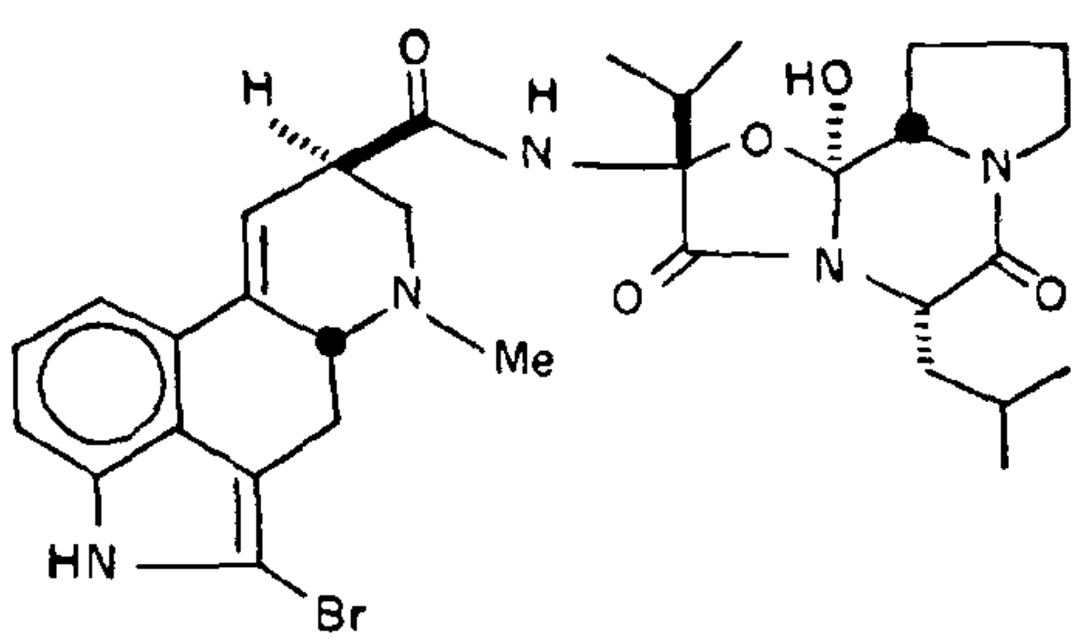
Vinca species have been greatly valued in the folk medicine of Europe and Middle East. Extensive pharmacological work on vincamine (7), first isolated by Schlittler in 1953 from *Vinca minor* L., has led to its introduction as a hypotensive agent and a mild sedative in Hungary (Devincan, 1970)[11,25]



Vincamine

(7)

Modification of natural substances is a powerful tool in devising useful drugs[26]. Semisynthetic steroids and prostanoids have already been referred to earlier. This approach has been very successful with ergot alkaloids, some of which have been in clinical use for quite sometime now, especially for relieving migraine headaches (ergotamine) and for obstetrical use (ergonovine)[27]. 2-Bromo derivative of ergocryptine, named bromocriptine (8) has now been introduced (1975) by Sandoz, under the trade name Parlodel, as an effective lactation antagonist and for treatment of morbus Parkinson[26,29].

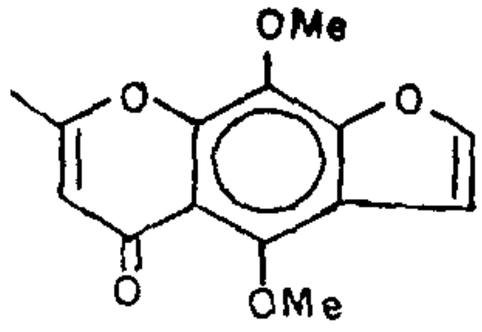


Bromocriptine

(8)

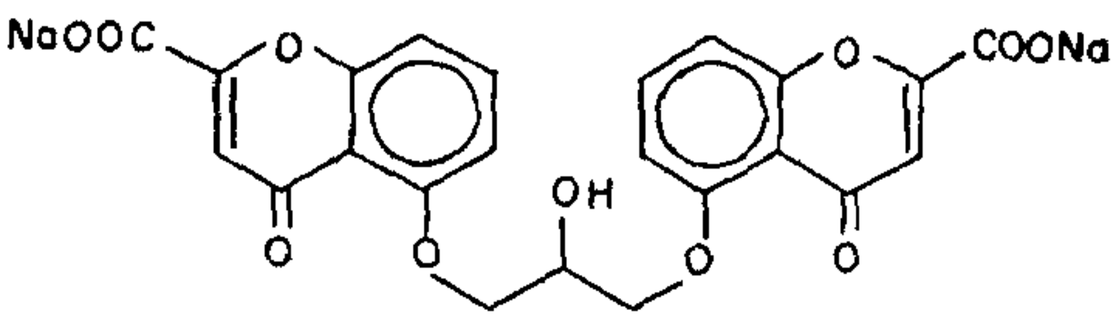
The development of a totally synthetic drug based on a natural product model can be illustrated by the following. An infusion of the leaves of the plant *Ammi visnaga* Lam. has been used in Egypt and neighbouring countries as a folk remedy for croup and colic. Its active principle was shown (1938) to be the furochromone, khellin (9) which proved (1947) to be a bronchodilator[30,31]. However, khellin was too toxic and several initial investigations aimed at improving its activity proved futile. Further investigations by another group finally led to the *bis*-derivative, disodium[31] cromoglycate (10), which has since been marketed as an anti-asthmatic drug under the trade name Intal (Fisons) first in France (1969) and later (1973) in US[22].

The drugs discussed so far represent the most important, though limited, contributions from research on higher plants. However, the total effort, including investigations carried out in universities and research institutions not belonging to pharmaceutical companies, has not been inconsiderable. A rather large number of new organic compounds exhibiting a variety of pharmacological activity have been isolated and cha-



Khellin

(9)



Disodium cromoglycate

(10)

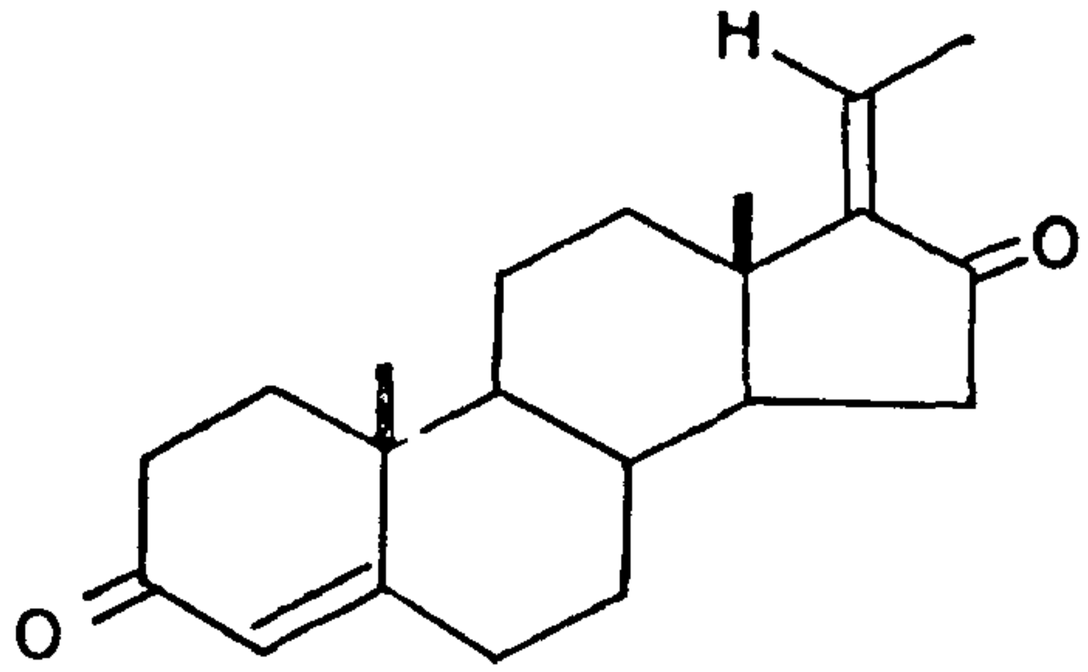
racterised. A major effort organised by National Cancer Institute (USA) has gone into random screening of higher plants for anticancer agents. Several interesting leads have been obtained. Recent reviews[32,33] and books[34,35] describe highlights of such investigations, covering not only higher plants, but also microbial products and marine flora and fauna. Other reviews[2,36,37] and a book[38] cover natural products showing various biological and pharmacological activities of interest in therapeutics. A number of programmes aimed at chemistry and biological activity of metabolites of marine flora and fauna have greatly enriched our knowledge on these subjects, and recent reviews on biological activity are available[39-41].

AYURVEDA AND DRUG DEVELOPMENT FROM NATURAL SOURCES

It is clear from the material presented so far, that most of the drugs from higher plants which have carved out for themselves an important place in modern medicine, invariably had their origin in the folklore and traditional systems of medicine of various cultures. In view of this, it would be worthwhile to evaluate the potential of this source for future drug development from natural sources, especially higher plants, and the well-established traditional systems of medicine which are still widely practiced in India and the neighbouring countries, and in South East Asia and China. Though these systems had, in the past, been viewed with skepticism by practitioners of Western system of medicine, there appears to be a fresh interest in these traditional systems[42,43].

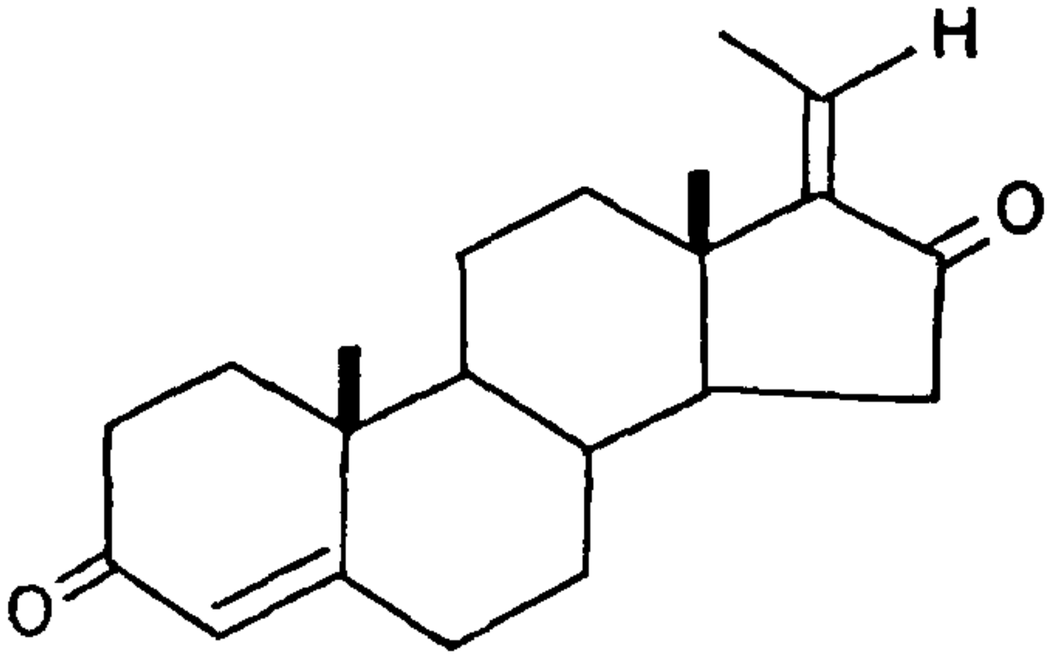
Ayurveda is still widely practiced in India. One estimate gives the number of Ayurvedic practitioners in India as 2,23,230 (1978). Plants form an important part of Ayurvedic pharmacopoeia. Charaka Samhita, one of the earliest treatises of Ayurveda (600 B.C.) lists a total of 341 plants and plant products for use in health management[44] Subsequent authors of later treatises (*Nighantu Granthas*), and there are over seventy of these, have extended the list of Ayurvedic single plant drugs to six hundred species of plants[45]. Thus, a definite basis exists for investigating these plants for biologically active constituents.

Many of these plants have received sporadic attention from Indian chemists, but it is only in recent years that two programmes were organised, though on a random search basis, for screening of Indian flora for biological activity. Though the outcome of Ciba-Geigy (Bombay) programme[46] is not known, summaries of results of the programme undertaken by Central Drug Research Institute (CDRI), Lucknow have been published[47]. CDRI investigations have yielded some leads, but nothing outstanding appears to have been achieved. Since this random search does include a large number of Ayurvedic crude drugs, do these results show that most of these so-called drugs have little scientific basis, or, is it that a new strategy for evaluating these plants is called for? It is felt that the paramount requirement is to devise a new, more effective strategy[48]. There are hundreds of Ayurvedic plant preparations which have withstood the test of time. It is necessary first to examine claims of these preparations as such. This should be done first on a clinical basis using all modern parameters. Once



Z - Guggulsterone

(11)



E - Guggulsterone

(12)

the claims of a particular preparation have been demonstrated by competent research, work should be undertaken to identify active principle/principles. This approach should take care of various imponderables, such as the question of right animal models, therapeutic action *via* prodrugs and immunopotentiation, the question of synergism and antagonism, factors which can greatly interfere with the outcome of work on traditional drugs and natural material in general. Isolation of reserpine from Sarpgandha (*Rauwolfia serpentina*) is a good example in favour of the above strategy. It was Vakil's work[49] on antihypertensive effect of Sarpgandha in man, that not only paved the way for the isolation of reserpine, but also resulted in the vindication of Ayurvedic claims.

Beginning with mid sixties a number of Ayurvedic single drugs have been screened for the claimed therapeutic effects. Results published so far tend to support Ayurvedic claims[50–52]. As an illustration, some of these plants are listed in table 2.

Our own experience with *Guggulu*, gum resin exudate from *Commiphora mukul* (Hook. ex Stocks) Engl. (Syn. *Balsamodendron mukul* Hook. ex Stocks) has been quite satisfactory[56]. The classical Ayurvedic literature claims its efficacy in a variety of metabolic disorders especially rheumatoid arthritis and obesity. We undertook investigations, in collaboration with the pharmacological group of Dr Swarn Nityanand at CDRI, Lucknow in an effort to track the claimed biological activity, especially hypocholesterolemic/hypolipaemic activity and isolate and characterise the pharmacologically active compound(s). It was soon found that neutral ethyl acetate-soluble fraction, which contained several ketones, exhibited high lipid-lowering activity. Further work led to the isolation of these compounds and it was found that two steroids, named *Z*-and *E*-guggulsterone 11, 12 are responsible for the hypolipaemic/hypocholesterolemic activity of *Guggulu*. The total ethyl acetate extract ("Guggulipid") has been standardised in terms of guggulsterones and has been selected for drug use. Phase III clinical trials are in progress and hopefully "Guggulipid" should reach the Indian market as a hypocholesterolemic drug by 1984/1985.

Thus, I believe that Ayurvedic drugs represent a treasure-trove waiting to be explored by all the modern techniques.

TABLE 2.
Some Ayurvedic Crude drugs with pharmacologically proven claims

No.	Plant (Botanical)	Plant (Sanskrit)	Type of activity
1	*Achyranthes aspera*	Apamarga	Diuretic[51]
2	*Acorus calamus*	Vacha	Tranquilizer[51]
3	*Artemisia vulgaris*	Nagadamni	Cardiac tonic[51]
4	*Butea frondosa*	Palasha	Anthelmintic[51]
5	*Bacopa monnierie*	Brahmi	"Memory"[51]
6	*Boerhaavia diffusa*	Punarnava	Antiinflammatory[51]
7	*Cassia fistula*	Suvarnake	Cathartic[51]
8	*Centella asiatica*	Mandukaparni	"Intelligence"[51]
9	*Curcuma longa*	Haridara	Antiinflammatory[53]
10	*Eugenia jambolana*	Jambu	Hypoglycemic[51]
11	*Euphorbia thymofolia*	Laghududhika	Antiasthmatic[54]
12	*Sida rhombifolia*	Mahabala	Anabolic[55]

OUTLOOK

At the end I wish to reemphasise the importance of natural products in modern medicine. Exploring mammalian chemistry represents a highly effective and powerful strategy for drug development. With the refinement of isolation techniques and methods of structure elucidation, and the availability of more effective biological screens, ethnotherapeutics may be expected to yield valuable drugs and lead compounds. Only a small fraction of higher plant species and aquatic flora and fauna have so far been explored and much remains to be done, to tap this versatile source of novel organic molecules with possible interesting biological properties. Genetic engineering has emerged as a powerful technology for economic production of biologically active complex molecules. Thus, natural products will continue to remain an important part of modern medicine into the foreseeable future. Eicosanoids, peptides, new microbial metabolites and semisynthetics appear to be all set to blaze the trial which started with the steroids and the antibiotics in the decades of 1940–1960, and continued into the following decades by their semisynthetic analogues. Finally it must be remembered that biological activity apart, economics and competition often determine if a therapeutically useful compound will or will not reach the market as a drug.

1. Farnsworth, N. R. and Bingel, A. S., In *New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity*, (eds) H. Wagner and P. Wolff, Springer-Verlag, Berlin 1977, p. 1.
2. Mitscher, L. A. and Al Shamma, A., *Annu. Rep. Med. Chem.*, 1980, **15**, 255.
3. Conover, L. H., In *Drug discovery*, (Advances in Chemistry Series, 108), *Am. Chem. Soc.*, Washington 1971, p. 33.
4. *Antibiotics*, (eds) M. J. Weinstein and G. H. Wagman, Elsevier, Amsterdam 1978.
5. Wiechert, R., *Angew. Chem. Int. Ed.*, 1979, **9**, 321.
6. Asolkar, L. V. and Chadha, Y. R., *Diosgenin and Other Steroid Drug Precursors*, Publication and Information Directorate, CSIR, New Delhi, 1979.
7. Hogg, J. A., In *Drug Discovery*, (Advances in Chemistry Series, 108), *Am. Chem. Soc.*, Washington 1971, p. 14.
8. Green, M. J. and Lutsky, B. N., *Annu. Rep. Med. Chem.*, 1976, **11**, 149.
9. Meienhofer, J., *Annu. Rep. Med. Chem.*, 1976, **11**, 158.
10. Kohen, F. Koch, Y. and Lindner, H. R., *Annu. Rep. Med. Chem.*, 1975, **10**, 284.
11. de Stevens, G., *11th International Symposium on Chemistry of Natural Products (IUPAC)*, Golden Sands, Bulgarian Academy of Sciences, 1978, Vol. 4, Part 1. p. 407.
12. Mohanan, J. J., *Annu. Rep. Med. Chem.*, 1982,

17, 229.
13. Leeney, T., *Chemistry and Industry*, 1982, 518.
14. *Inside R & D*, 1982, Nov. 10, p. 2.
15. Bindra, J. S. and Bindra, R., *Prostaglandin Synthesis.*, Academic Press, New York, 1977.
16. Nelson, N. A. Kelly, R. C. and Johnson, R. A., *Chem. Engg. News.*, 1982, Aug. 16, p.30.
17. Bartmann, W. and Beck, G., *Angew. Chem. Int. Ed.*, 1982, **21,** 751.
18. Ackroyed, J. and Scheinmann, F. *Chem. Soc. Rev.*, 1982, **11,** 321.
19. Cushman, D. W. and Ondetti M. A., *Chemtech.*, 1982, **12,** 620.
20. Bloom, B. M., In: *Drug discovery*, (Advances in Chemistry Series, 108), *Am. Chem. Soc.*, Washington 1971, p. 176.
21. See e.g: Kupchan, S. M., In: *Drug discovery*, (Advances in Chemistry Series, 108), *Am. Chem. Soc.*, Washington 1971, p. 1.
22. Sittig, M., *Pharmaceutical Manufacturing Encyclopedia*, Noyes Data Corporation, New Jersey, 1979.
23. *Materials and Technology*, 741 Longman, London, 1972, Vol. 5, p. 741.
24 *Annual Drug Data Report*, Vol. III–1981, J. R. Prous. Barcelona 1981.
25. *The Vinca Alkaloids* (eds) W.I. Taylor and N. Farnsworth, Dekker, New York, 1973.
26. Thies, P. W., In: *New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity*, (eds) H. Wagner and P. Wolff, Springer-Verlag, Berlin 1977, p. 266.
27. *Remington's Pharmaceutical Sciences*, (ed) A. Osol, 887, 888. Mack Publishing Co., Easton, 1980, p. 405.
28. *Materials and Technology*, Vol. V, Longman, London 1972, p. 735
29. *Annual Drug Data Report*, Vol. II-1979/1980. J. R. Prous, Barcelona, 1979.
30. Schmid, H., *Fortschr. Chem. Org. Naturstoffe*, 1954, **11,** 124.
31. Lunt, E., In: *Progress in Pharmaceutical Research* (ed.) K. R. H. Wooldridge, Blackwell, Oxford, 1982, p. 62.
32. Cordell, G. A., In: *New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutic Activity* (ed.) H. Wagner and P. Wolff, Springer-Verlag, Berlin, 1977, p. 54.
33. Struk, R. F., *Annu. Rep. Med. Chem.*, 1981, **16,** 137.
34. *Anticancer Agents based on Natural Product Models* (eds) J. M. Cassady and J. D. Douros, Academic Press, New York, 1980.
35. *Antitumor Compounds of Natural Origin* (ed) A. Aszalos, CRC Press, Boca Raton, 1982.
36. Mitscher, L. A., In: *Antibiotics* (eds) M. J. Weinstein and G. H. Wagman, Elsevier, Amsterdam 1978, p. 463.
37. de Souza, N. J., Ganguli, B. N. and Reden, J., *Annu. Rep. Med. Chem.*, 1982, **17,** 301.
38. *New Natural Products and Plant Drugs with Pharmacological Biological or Therapeutical Activity* (eds) H. Wagner and P. Wolff, Springer-Verlag, Berlin 1977.
39. Baslow, M. H., *Marine Pharmacology*, R. E. Krieger, Huntington, 1977.
40. *Drugs and Food from Sea* (eds) P. N. Kaul and C. J. Sindermann, The University of Oklahoma, Norman, 1978.
41. *Marine Algae in Pharmaceutical Sciences*, (eds) H. A. Hoppe, T. Levring and Y. Tanaka. Walter de Gyuyter, Berlin, 1979.
42. *Herbal Pharmacology in Peoples Republic of China*, National Academy of Sciences, Washington, 1975.
43. *Realms of Ayurveda*, (ed) S Sharma, Arnold-Heinemann (India), New Delhi, 1979.
44. Ray, P. and Gupta, H. N., *Charaka Samhita (a Scientific Synopsis)* National Institute of Sciences of India, New Delhi, 1965.
45. Namjoshi, A., In: *Realms of Ayurveda*, (ed) S. Sharma, Arnold-Heinemann, India, New Delhi 1979, p. 217.
46. Desai, H. K., *et al., Indian J. Chem.*, 1973, **11,** 1 and earlier references cited therein.
47. Dhawan, B. N., Patnaik, G. K., Rastogi, R. P., Singh, K. K. and Tandon, J. S., *Indian J. Exp. Biol.*, 1977, **15,** 208. and earlier references cited Bulgaria 1981, p. 168.
48. Sukh Dev, *Arogya - J. Health Sci.*, 1977, III, 121.
49. Vakil, R. J., *British Heart J.* 1949, **11,** 350.
50. *ICMR Bulletin*, 1972, vo. 2 no. 5,6.
50. *ICMR Bulletin*, 1972, Vol. 2 No. 5,6.
51. *Medicinal Plants of India* (eds) G. V. Satyavati, M. K. Raina and M. Sharma, Vol. I Indian Council of Medical Research New Delhi 1976.
52. Atal, C. K., in *Indo-Soviet Symposium on the Chemistry of Natural Products*, Pune, Plenary Lectures, Indian National Science Academy, New Delh,i 1982, p. 99.
53. Shukla, Y. N., Tandon, J. S. and Dhar, M. M., *Experientia*, 1969, **25,** 357.
54. Sharma, G. D. and Sharma, P. V., *J. Res. Ind. Med.* 1971, **6,** 118.
55. Prakash, A. and Sharma, P. V., *Bull. Medico-Enthno-Botanical Res.* 1981, **2,** 226.
56. Sukh Dev., In: *First International Conference on the Chemistry and Biotechnology of Biologically Active Natural Products,* Proceedings Vol. 1, Varna, Bulgaria 1981, p. 168.