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MEGHNAD SAHA MEDAL LECTURE—1987

AYURVEDA AND MODERN DRUG DEVELOPMENT*

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I AM keenly aware of the honour done to me by the Academy in selecting me for the Meghnad Saha Medal for the year 1987. I feel all the more honoured, as it links me with the name of one of our most illustrious scientists, who was at once a great intellectual and a dedicated humanist.[1] I propose to speak to you to-day on *Āyurveda* and Modern Drug Develoment, a topic relevant to the current developmental needs of the country, and an area in which we have been interested for the past two decades or so.

Before proceeding further, it seems appropriate that I define the term modern drug, at least, in the context of the present lecture. The term drug has been defined in legal terms in various regulatory manuals,[2] but such definitions are not relevant for the present purpose. In the absence of a readily accessible (to me) suitable definition, I may define modern drug as *a clinically efficacious chemical entity or, mixture of synthetic or natural origin, administered as such or admixed with other entities or vehicles, and capable of 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 medicine. Thus, a preparation based on a natural product and shown to be clinically efficacious and produced in a standardized form becomes a modern drug.

ROLE OF NATURAL PRODUCTS IN MODERN MEDICINE

At present, it is generally believed by the lay public that most of the mordern drugs are of synthetic origin, and, that drugs of natural provenance are no longer important. This, in fact, is not true.[3] An analysis of prescriptions dispensed from community pharmacies in USA was carried out[4] in 1973, and this showed that as many as 41 per cent prescriptions contained one or more products of natural origin as the therapeutic agent. Of these prescriptions, 25 per cent were based on drugs from higher plants, some 13 per cent represented metabolites of microbes and about 7 per cent were of animal origin. The total value of these prescriptions was

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estimated to be of the order of US $ 5 billion (Rs. 6500 crores). Another later reference[5] mentions that 25 per cent of the 200 most frequently prescribed drugs in the USA, were of natural origin. The situation would appear to be similar for many other countries including India, and as a matter of fact, this figure may even be higher for Soviet Union, Germany, Italy, China and Japan. Thus, natural products represent an important segment of modern drug armamentarium.

As already mentioned, drugs of natural provenance have been obtained from three different sources : higher plants, microbes and animals. Hormones, enzymes, antibiotics used in medicine to-day owe their origin to studies on animals and microbes. These contributions are some of the most important in modern medicine. However, in the context of this lecture we are mostly concerned with drugs from plants. More than 75 pure compounds derived from higher plants find their place in modern medicine, and some of the traditional ones are shown in Table I. However, it may be noted that ψ-ephedrine, ephedrine, emetine, caffeine, theobromine, theophylline and papaverine are now mostly produced synthetically for economic reasons. All compounds listed in Table I were introduced in modern medicine between 1850 and 1950. Beginning with 1950 science has made rapid, accelerating strides along all its facets and medicine has been no exception. Breakthroughs in a discipline often result from outstanding progress in related areas. Advances in physics, chemistry and biology, coupled with progress in isolation technology, analysis, characterisation and structure recognition have led to great advances in drug development. Thus the period 1950-70 saw the

TABLE I

Important traditional active plant principles[a]

No.	Drug	Plant source
1	Codeine	*Papaver somniferum*
2	Atropine	*Hyoscyamus muticus*
3	ψ-Ephedrine[b]	*Ephedra* spp.
4	Ephedrine[b]	*Ephedra* spp.
5	Hyoscyamine	*Hyoscyamus muticus*
6	Digoxin	*Digitalis lantana*
7	Hyoscine	*Datura metel*
8	Digitoxin	*Digitalis purpurea*
9	Pilocarpine	*Pilocarpus jaborandi*
10	Quinidine	*Cinchona* spp.
11	Quinine	*Cinchona* spp.
12	Emetine[b]	*Cephaelis* spp.
13	Caffeine[b]	*Thea sinensis*
14	Theobromine[b]	*Theobromo cocao*
15	Theophylline[b]	*Coffea arabica*
16	Papaverine[b]	*Papaver* spp.
17	Colchicine	*Colchicum autumnale*

[a]Based on ref. 4.

[b]Now mostly produced synthetically.

introduction of approximately one hundred basic new drugs in the U.S. market.[6] However, this list contained no more than five drugs (reserpine, deserpidine, rescinnamine, vinblastine and vincristine) derived from higher plants. Though, these compounds represent outstanding breakthroughs in modern medicine, the overall contribution from higher plants is clearly not impressive. This is attributed mainly to the fact that many pharmaceutical companies have been reluctant to invest in a major way, because of problems associated with plant collection, standardization and supply. However, the total effort, including investigations carried out in universities and research institutions not belonging to pharmaceutical companies, expended on biologically active compounds from plants has not been inconsiderable. A rather large number of new organic compounds exhibiting a variety of pharmacological activity have been isolated and characterized.[5,7-9] To emphasize the worthiness of these investigations, I have listed in Table II, types of biological/pharmacological activities (except anticancer) reported for compounds

TABLE II

Biological activities encountered (1977–79) *during screening of higher plants for active compounds*

No.	Biological Activity	Number of Biologically Active compounds Isolated
1	Antibacterial	17
2	Antifertility	2
3	Antifungal	14
4	Antiinflammatory	7
5	Antiviral	3
6	Antiulcer	3
7	Cardiovascular	5
8	CNS Depressant	5
9	Hypoglycemic	1
10	Hypotensive	13
11	Hypocholesterolemic	4
12	Immunosuppressive	1
13	Spasmolytic	3

from higher plants, during the three year period, 1977–79, covered in a review.[6] The economic importance of such studies can be gauged from the fact that in 1975 alone over 400 patents were issued for substances isolated from plants alone.[4]

Quite often, biologically active natural products have served as models for improved drugs. Corticosteroids[10] and semisynthetic antibiotics[11] are excellent examples.

Thus, biologically active compounds from nature promise to remain an important part of modern medicine into the foreseeable future.

STRATEGIES FOR DRUG DISCOVERY FROM NATURE

How have drugs from nature been discovered ? Various strategies have proved useful and these may be classified[3] into following four categories :

(*a*) Study of human (and animal) biochemistry and physiology—recognition of hormones, bioregulators, co-factors, enzymes and other biomacromolecules ;

(*b*) Random search—plants, microbes, marine flora and fauna ;

(*c*) Chemotaxonomic considerations; and

(*d*) Ethnotherapeutics—folklore, traditional systems of medicine.

It will be worthwhile to briefly elaborate on these, and assess their worthiness for future drug discoveries.

Study of *mammalian chemistry* is a powerful tool for the development of new therapeutic agents. Use of hormones, vitamins and enzymes in health management has been the direct outcome of these efforts, which represent high mark of scientific achievement for the second quarter of this century. Amongst the hormonoes which were introduced in clinical usage during 1950–60, may be mentioned insulin, thyroxine, sex hormones, adrenocortical hormones and oxytocin. Special attention may be drawn to the steroidal sex and adrenocortical hormones,[10,12] the study of which dominated drug development from natural sources during the period 1950–65, when several semisynthetic analogues with superior therapeutic activity were developed and launched.[13] Since then, prostaglandins[14] and polypeptide hormones[15] have occupied dominating attention of several groups, because of much commercial potential. Polypeptide hormones are special targets for production by recombinant DNA and hybridomas technologies.[16-17] This powerful combination is all set to alter fundamentally biomedical research methodologies.

Random search for bioactive compounds from higher plants, lichens, bryophyta, microbes, and marine flora and fauna, has received extensive attention. Random search has proved most fruitful in the discovery of antibiotics from a variety of microorganisms.[18,19] Extensive researches have also been carried out on plant materials for anticancer agents and though valuable leads have been obtained,[20,21] no drug has as yet reached the market *via* this strategy.

Chemotaxonomic considerations come into play once we know about the occurrence of a bioactive material in a plant or microorganism. Discovery of new antibiotics was greatly aided by these considerations.[18]

The fourth strategy is based on the *ancient medicinal knowledge* of various tribes, cultures and civilizations. If one looks at how the traditional plant drugs (cf Table I) 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 a particular cure in some folklore. Table III illustrates this point convincingly. Even after this classical plant drug discovery era, most of the important plant drugs have been discovered through folklore or traditional systems of medicine. Reserpine, the discovery of which in 1952, provided a distinct fillip to plant drug research, had its origin in *Āyurveda* : its source *Sarpagandha* (*Rauwolfia serpentina*) is a well-recognized drug for the treatment of hypertension, insomnia and insanity,

TABLE III

Ethnotherapeutics and traditional modern drugs

No.	Drug	Basis of investigation
1	*Codeine, morphine* etc.	Opium, the latex from *Papaver somniferum* used by ancient Sumerians, Egyptians and Greeks for treatment of headaches, arthritis, for inducing sleep.[22,23]
2	*Atropine, hyoscyamine*, etc.	*Atropa belladona, Hyoscyamus niger* (henbane) were important items of Babylonium folklore.[24]
3	*Ephedrine*	Crude drug *Ma-huang* (astringent yellow) derived from *Ephedra sinica* had been used by Chinese for respiratory ailments since 2700 B.C.[24]
4	*Quinine*, etc.	*Cinchora* spp. were used by Peruvian Indians for the treatment of fevers.[22,24]
5	*Emetine*	Brazilian Indians and several other South American tribes used roots and rhizomes of *ipecacuanha* (*Cephaelis* spp.) to induce vomitting and cure dysentery.[22,24]
6	*Caffeine*, etc.	These are major constituents of tea, coffee and cocoa used for preparing stimulating beverages in different parts of the world since many centuries ago.
7	*Colchicine*	Use of *Colchicum* in the treatment of gout has been known in Europe since 78A.D.[24]
8	*Digoxin*, etc.	*Digitalis* leaves were being used in heart therapy in Europe during the 18th century.[22]

in the Ayurvedic system of medicine.[25,26] The discovery of two dimeric indole alkaloids, vinblastine and vincristine, valuable for the treatment of Hodgkin's disease, lymphosarcoma and leukemia in children, from the periwinkle plant (*Catharanthus roseus*), is again the result of folklore remedy investigation, though in a different way. Work on this plant was taken up for its alleged hypoglycemic activity as per Jamaican folklore![3,25] Podophyllum resin has been used by American Indians for treatment of cancer[27]; its active compound, podophyllotoxin, is the basis for etoposide and teniposide, anticancer agents currently being used against testicular cancer, small-cell lung cancer and lymphomas.[28]

From the above analysis it is clear that ethnotherapeutics provide a powerful and more effective strategy for the discovery of clinically useful compound from plant kingdom.

ZHONG YAO—THE CHINESE SYSTEM OF MEDICINE

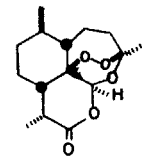
The above conclusion gets reinforced when one surveys the results of modern investigations on Chinese medicine. Chinese medicine (*Zhong yao* in Chinese, *kanpo* in Japanese) has been practiced in China and the neighboring countries since

more than 2000 years ago, and was apparently first systematized in *Shang Han Tsu Ping Lun*, a 16-volume compendium, possibly compiled by Chang Chung-Ching in the second century A.D.(142–210). This work records eighty crude drugs, while another later(456–536) compilation, *Shin-Nung Pen T'sao Ching*, of Tao Hung-Ching, describes 365 crude drugs.[29] Though the Chinese system of medicine, like other traditional systems of medicine had, in the past, been viewed with skepticism by the practitioners of Western system of medicine, there appears to be a healthy interest now.[30] The *Pharmacopoeia of the People's Republic of China*, issued in 1978 describes 882 crude drugs of which 637 are of plant origin. *Japanese Pharmacopoeia X* released in 1981, contains 102 plant drugs, of which only 29 are crude drugs used in Western medicine.[30] The incorporation of a rather large number of plant drugs in Chinese and Japanese recent pharmacopoeia is the direct consequence of modern investigations on Chinese medicine.

Chinese crude drugs have been the subject of intense modern scrutiny during the past two decades or so, mostly at the hands of Chinese.[32–34] Outstanding results have been obtained, essentially confirming many claims of the ancients. Several of these results have received international attention and acclaim. Thus, the traditional Chinese antimalarial drug, *ginghao* (aerial parts of *Artemisia annua*) has furnished a potent antimalarial, artemisinine (*qinghaosu*) (*1*), active against *Plasmodium vivax* and *P. falciparum* when given orally or intramuscularly.[35,36] This has been commercialized in China.[32] A simple derivative of artemisinine, called artemether (*2*), has been found to be superior for treatment of tertian and cerebellar malaria and is undergoing clinical evaluations.[34,37,38] Ginseng, which comprises roots of *Panax ginseng* is highly valued in the Orient as a tranquilizer, as an extender of memory, and as a general tonic. Modern investigations, mostly conducted by the Japanese have led to the isolation of a large number of triterpene glycosides (ginsenosides), mainly based on dammarane skeleton (e.g. ginsenoside Rb_2, *3*).[29,33,39,40] Several of these ginsenosides have been shown to exhibit a variety of pharmacological activity, such as increased DNA, RNA, protein and lipid synthesis in bone marrow cells, and suppression of cyclic AMP levels.[39,41] World market for ginseng and its products has been estimated (1980) at 1700 tonnes valued at around US $ 70 million.[42]

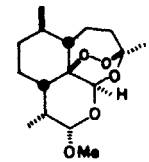
The announcement by the Chinese, in 1978, that gossypol (*4*), the yellow (rather toxic) pigment of the cotton plant (*Gossypium* spp.) is an effective male contraceptive, was received by the international medical community with much excitement. Since then, the results have been confirmed in several studies outside China, and the compound is under active further investigation.[33,43,44]

Other interesting drugs, based on the Chinese system of medicine, and which are being marketed in China are : indirubin (*5*) from leaves of *Baphicacanthus cusia* as an antineoplastic agent; agrimorphol (*6*) from winter buds of *Agrimonia pilosa* as a potent anthelmintic; tetramethylpyrazine (*7*), a component of *Ligusticum chuanxiong*, for treatment of occlusive blood vessel diseases, such as cerebral embolism; lignans (e.g. schizandrin C, *8*) from fruits of *Schizandra chinensis* as a



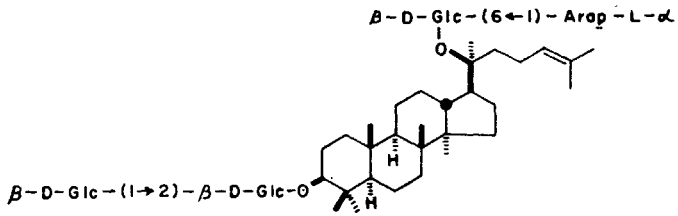
Artemisinine

1



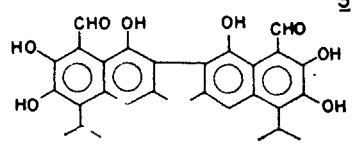
Artemether

2



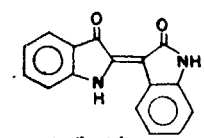
Ginsenoside - Rb_2

3



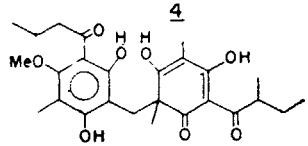
Gossypol

4



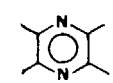
Indirubin

5



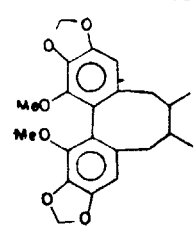
Agrimorphol

6



Tetramethylpyrazine

7



Schizandrin - C

8

protective agent against liver damage.[32,34] Trichosanthin, a well-characterized plant protein from the roots of Cucurbitaceae plant *Trichosanthes kirilowii* is being used in China as an abortifacient.[35]

Though several other examples from Chinese literature can be cited, the main purpose of citing these results, namely highlighting the importance of ethnotherapeutics, should have been served. Let us now have a look at our traditional system of medicine, that is Ayurveda, and evaluate its potential as a source for modern drug development.

Ayurveda and Drug Development from Plant Sources

Before proceeding further it appears appropriate to first present a brief introduction to *Āyurveda*. This may sound redundant as I am speaking to an audience of Indians in India. However, the unfortunate fact remains that many of us have not cared much to learn about our own heritage, and often look upon it with mistrust and disdain—the direct consequence of our system of education started by the British (understandingly) and perpetuated, since 1947, by our own people!

Āyurveda is the ancient Indian system of health-care, both physical and mental. The word *Āyurveda* is derived from *Ayus(r)*, meaning life, and *Veda*, meaning knowledge. Thus *Āyurveda* literally means "Science of life". This covers the art of living. Health, in *Āyurveda*, has been defined as a well-balanced metabolism plus a happy state of being. Disease has been considered four-fold, as emanating from (i) body (ii) mind, (iii) external factors, and (iv) natural intrinsic causes. The definition of treatment, in *Āyurveda*, covers a salubrious use of drugs, diets and practices.[45]

Pharmaceutics occupies an important place in *Āyurveda*. 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 *Rigveda* and *Atharvaveda*, dating back to second millennium B.C. *Charaka Samhita* (~900 B.C.) is the first recorded treatise on *Āyurveda*; it consists of eight sections divided into 150 Chapters, and describes 341 plants and plant products for use in medicine. Therapeutics (*Kayachikitsa*) is the hallmark of this works.[46,47] The next landmark in *Āyurveda* is *Sushruta Samhita* (~600 B.C) with 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 drugs. Sushruta, the Father of Surgery, lived and practiced surgery in Varanasi, some 2500 years ago.[48,49] The next important authority in *Āyurveda*, after Charaka and Sushruta, was Vagabhatta of Sind, who practiced about 7th Century A.D. His works, *Aṣtanga Hridaya*, is considered unrivalled for principles and practice of medicine. *Aṣtanga Hridaya*, is described in six sections covering 120 Chapters, and contains 7444 verses; the entire book is in verse.[46] Charaka, Sushruta and Vagabhatta are the *Vrihat Traya* (Powerful Triad) of *Āyurveda*. *Madhava Nidana*, consisting of 69 chapters and 1,552 verses, is the next important landmark. This work excels in diagnosis. It was written in 12th century by Madhava, the famous Vidyaaranya of Vijayanagar. Sarangdhara (14th century), the author of *Sarangdhara Samhita* systematised Ayurvedic *materia medica*; this work consists of three parts, 32 chapters and 2,500 verses. The last celebrated writer on Hindu medicine is Bhava Mishra of Magadha, and his treatise *Bhava Prakasha* written ~1550 is held in high esteem by the modern Ayurved practitioners. It has three sections containing 10,831 verses; approximately, 470 medicinal plants are mentioned.[46,50] Madhava, Sarangdhara and Bhava Mishra have been referred to as the *Laghu Traya* (Junior Three) of *Āyurveda*. Besides these monumental treatises, a rather large

TABLE IV

Eight branches of Āyurveda

No.	Branch	
	Sanskrit designation	Remarks
1	*Kayachikitsa*	Therapeutics: all aspects
2	*Shalakyatantra*	Diseases of eyes, ears, nose, tongue, oral cavity, throat
3	*Shalyatantra*	Surgery
4	*Kaumarabhritya*	Paediatrics : anti-natal and post-natal baby care, and care of mother before conception and after pregnancy : diseases specific to children and their treatment
5	*Agadtantra*	Toxicology : deals with poisons of various types and their antidotes; environmental and water pollution
6	*Bhutvidya*	Psychiatry
7	*Rasayana*	Knowledge of tonics and processes for arresting the process of mental and physical decay; rejuvenation
8	*Vasikaranatantra*	Knowledge of virilifics: dealing with lost or diminished virility, potency and procreative ability

TABLE V

*Classification of plant drugs (Charaka)**

No.†	Group	
	Sanskrit name	Remarks
1	*Jivaniya*	Promoting longevity
3	*Lekhaniya*	Anti-obesity
6	*Dipaniya*	Promotor of digestion
7	*Balya*	Promoting strength
8	*Varnya*	Complexion-promoting
15	*Krmighna*	Anthelmintic
17	*Stanyajanana*	Galactogogue
23	*Vamanopaga*	Emetic
24	*Virechanopaga*	Purgative
35	*Mutravirechaniya*	Diuretic
36	*Kasahara*	Antitussive
38	*Svayathuhara*	Antiinflammatory
39	*Jvarahara*	Febrifuge
47	*Vedanasthapana*	Analgesic
50	*Vayahsthapana*	Anti-ageing

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

number of (>70) *Nighantu Granthas* or pharmacy lexicons have been written, mostly between 7th and 16th century.[51,52] *Raja Nighantu* by Narhari Pandita, and

Madanpala Nighantu by Madanpala are considered as masterpieces on medicinal herbs.[46]

Eight branches of medicinal knowledge (*Āṣtanga*) have been recognized in *Āyurveda* from ancient times. The lists given by Charaka, Sushruta and Vagabhatta are identical, though different in order.[49] Table IV gives this classification which is relevant to this day. Drugs have been classified on the basis of their physiological action.[53] For example, Charaka has divided plant durgs into fifty groups according to the actions of their decoctions. Table V gives part-list of this classification,[47] by way of illustration.

This introduction should suffice to emphasize that Ayurveda was a well-organised science of its times and this store-house of knowledge and information offers a unique opportunity for further exploration by all the powerful and subtle techniques of modern science. In the present context, the Ayurvedic plant drugs deserve to be explored for modern drug development.

It may be mentioned that the Ayurvedic texts were translated into Greek (300 B.C.), Tibetan and Chinese (300 A.D.), Persian and Arabic (700 A.D.), and languages of other Asian people.[54–56]

Modern Investigations on Ayurvedic Drugs

With the introduction of western scientific methods in India, Ayurvedic drugs and other Indian plants with alleged medicinal properties came under some sort of scrutiny. Many plants and their products came to be examined by chemists and medical people, though without any significant collaboration between the various disciplines. A fairly comprehensive account of these researches covering approximately 100 plant drugs, is given in Col. Ram Nath Chopra's now classic, Indigenous Drugs of India (1958).[57] These investigations did result in the confirmation of some attributes of these drugs.

Around 1964 systematic screening of Indian flora was undertaken at CDRI, Lucknow,[58] and CIBA-Geigy Research Centre, Bombay.[59] One really does not know the outcome of CIBA programme, as for obvious reasons, the results have not been made public. CDRI, on the other hand, regularly published the results of its findings. During a period of some 20 years, CDRI screened approximately 2500 plants for a variety of activities. Important leads appear to have been obtained and the results have been summarized in a recent publication.[60]

In 1961, the then Central Council of Ayurvedic Research (CCAR), Government of India, arranged a conference of reputed Ayurvedic Vaidyas to prepare a list of effective Ayurvedic plants. A list of 190 drugs, thus, emerged. Next, a Composite Drug Research Scheme (CDRS) was formulated by the Ministry of Health in collaboration with the Indian Council of Medical Research (ICMR), the then CCAR, and the Council of Scientific and Industral Research (CSIR). This was launched in 1964, and was technically under the administrative control of ICMR till April 1970, when the newly created Central Council for Research in

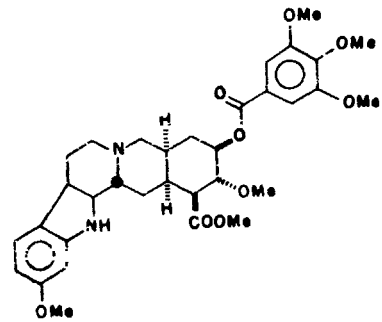
Indian Medicine & Homeopathy took charge of the scheme. Under this scheme nine circuits were set up in different parts of the country. Each circuit comprised four units, namely clinical (both Ayurvedic and Modern), pharmacognosy, chemical and pharmacological.[61] This scheme appears to have operated through the seventies. Results of these investigations have been published in two books,[62,63] besides in articles in other professional journals.

Besides the above major efforts, work on Indian medicinal plants has also been carried out in various universities and research institutes, and results reported in professional journals. The two above-mentioned books[62,63] also summarise these findings.

How does one evaluate the impact of these efforts spanning several decades ? To my mind, the study of medicinal plants has clearly one objective, namely, development of improved and better drugs for health-care. Training of personnel, discovery of new chemical entities or recognition of new concepts, though important in their own right, can only be considered as spin-offs and incidental to the main purpose. Viewed thus, the impact of these efforts has been rather dismal. Nothing from the above major programmes has as yet reached the market !

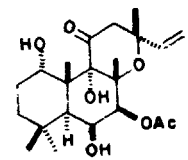
However, it may be pointed out that in 1953, reserpine (*9*) briefly alluded to earlier, and a minor alkaloid of Ayurvedic drug *Sarpagandha*, was introduced as an antihypertensive drug in modern medicine.[64] Though, the starting point for this development was a publication[65] by Dr R. J. Vakil of Bombay, the credit for successful development of a modern drug from this lead goes entirely to CIBA, Switzerland. A second contribution from *Ayurveda* is the very recent marketing of a hypolipaemic drug based on *guggulu*, the gum-resin of *Commiphora mukul*.[66] I shall shortly discuss this in some detail. Besides this, I must also mention forskolin (colenol, *10*), which was isolated independently by two different groups, one working at CDRI[67,68] and the other at Hoechst Research Centre, Bombay.[69] This compound activates hormone sensitive adenylate cyclase, thus potentiating cyclic AMP levels and providing a new mechanism to potentiate hormonal responses. Forskolin is a potent hypotensive agent, and also appears to be a valuable agent for the treatment of glaucoma. Several other therapeutic applications have been visualized.[70–72] Forskolin was isolated from roots of *Coleus forskohlii* (syn. *C. barbatus*), a plant not mentioned in classical Ayurvedic literature. As a matter of fact roots of this plant (Gujarati, *Garmal*) are pickled and consumed in Gujarat.[73]

It may be instructive at this stage to analyse the reasons for this rather dismal performance. Development of a marketable drug is a complex business requiring an above-critical outlay of inputs (personnel, materials, expertise) and an effective organizational set-up. Judged from this angle, work in the universities, medical colleges and small institutes can never lead to fruition. No wonder India missed discovery of reserpine. The CDRS, though well-conceived, proved impractical, as there was, despite best efforts, little co-ordination for several reasons mentioned



Reserpine

9



Forskolin

10

elsewhere.[74] Though many Ayurvedic claims could be confirmed, the leads were not pursued further. Work at CDRI should have led to more fruitful consequences. Though, important leads were noted, somehow they could not be developed further, possibly because work undertaken was of a vast magnitude, without proper focus.

How does Ayurvedic materia medica, to which we have made some detailed references earlier, emerge from all this ? Does starting with a plant, reported in *Ayurveda* for a particular application, offer any additional or special advantage for drug development ? A clear cut answer is not forthcoming from the above. While working as part of "Circuit-I" of CDRS, at NCL, Poona, we had occasion to investigate *shatavari* (*Asparagus racemosus*) and *punarnava* (*Boerhaavia diffusa*), and were happy to see confirmation of ancient claims. This reinforced my earlier views that Ayurvedic drugs which have withstood the test of time must have something in them. The (late) Dr C Dwarakanath, who was overseeing the work of CDRS, suggested that we also work on *guggulu*, which according to him, is valued in *Ayurveda* as an anti-inflammatory drug and for correcting lipid disorders. He was all the more keen, since according to general screening at CDRI, nothing worthwhile had been found in this drug, but he felt convinced that a different approach than that adopted at CDRI was called for.[75,76] He felt strongly, and I fully concurred with him, that while screening Ayurvedic drugs we should specially look for the activity for which it is recommended in Ayurveda. Soon after that, I met Dr Nitya Anand (CDRI) and he readily agreed to collaborate in this work. This offered a good opportunity to answer the question which I posed earlier : does any lead from Ayurveda offer an advantage in drug development ? From the story I am about to unfold an unequivocal yes did emerge !

GUGGULU, AN ANCIENT AYURVEDIC DRUG

Guggulu is the gum-resin exudate of a small tree, *Commiphora mukul* (syn. *Balsamodendron mukul*) belonging to the family Burseraceae. This tree is endemic

to India and is found wild in semi-arid regions of Rajasthan, Madhya Pradesh, Gujarat and Karnataka. In its natural setting the tree remains essentially denuded of its foliage for most of the year. On injury, the plant exudes a yellowish gum-resin, which soon solidifies to an agglomerate of tears or stalactitic pieces with balsamic odour. These trees are tapped commercially, the average yield of gum-resin per tree being ~700-900g/year, and the collection is done during the cold season. This is the *gugglu* of commerce.[77]

Guggulu is highly valued in *Ayurveda*. It is mentioned in *Atharva Veda*. It is specially recommended for the treatment of, obesity, lipid disorders and rheumatoid arthritis (Sushruta, Vagabhatta). Fig. 1 reproduces the Sanskrit *shloka*, given in *Bhava Prakasha*, describing the various attributes of *guggulu*. Thirtythree compound preparations containing *guggulu* as a component are described in *Bhava Prakasha*.[78]

Modern pharmacological studies on the crude drug and some of its fractions had tended to support the claims of Ayurveda. Thus, anti-arthritis and anti-inflammatory activities were confirmed by Gujral and co-workers.[79,80] Dwarakanath, Satyavati and co-workers were able to establish the value of *guggulu* in lipid disorders, especially as a hypocholesterolemic and hypolipemic agent.[81-84] These findings were soon confirmed by other workers.[85,86] Thus, when we were introduced (1969) to *guggulu*, sufficient basis existed for undertaking detailed chemical and biological investigations.

Chemical work was soon undertaken at NCL, Poona and was later continued at Malti-Chem Research Centre, Vadodara. All biological work was carried out at CDRI, Lucknow under the leadership of Dr Nitya Anand and Dr Swarn

गुग्गुलुर्विशदस्तिक्तो वीर्योष्णः पित्तलः सरः ।
कषायः कटुकः पाके कटुरूक्षो लघुः परम् ॥
भग्नसंधानकृद्वृष्यः सूक्ष्मः स्वर्यो रसायनः ।
दीपनः पिच्छिलो बल्यः कफवातव्रणापची ॥
मेदो मेहांश्च वातास्रक्लेदकुष्ठामामरुतान् ।
पिडिकाग्रन्थिशोफार्शोगण्डमालाकृमीञ्जयेत् ॥
माधुर्याच्छमयेद्वातं कषायत्वाच्च पित्तहा ।
तिक्तत्वात्कफजित्तेन गुग्गुलुः सर्वदोषहा ॥

FIG 1 *Shlokas* from *Bhava Prakasha* giving attributes of *Guggulu*.

Nityanand. Important results were periodically reported in seminars[88,89] or other publications.[90–94] During the course of these investigations, a significant number of publications on biological activities of *guggulu* or its fractions were published by other groups.[62,95]

Segregation of Guggulu *and Isolation of Compounds with Hypolipemic Activity*

After considerable effort, involving biological screening at each stage, a viable separation scheme was evolved and this is shown in Fig. 2. The ethyl acetate soluble portion, which constitutes ~ 45 per cent of the gum-resin, carries both the hypocholesterolemic and anti-inflammatory activities. The insoluble part, which represents the carbohydrate gum portion of the gum-resin studied earlier by Bose and Gupta,[96] was found to be toxic and hence, was not investigated further. The ethyl acetate-soluble part was chemically exceedingly complex. It was, next, separated into bases, acids and a neutral cut. The neutral fraction carries practically all hypocholesterolemic activity, while the acidic cut showed significant

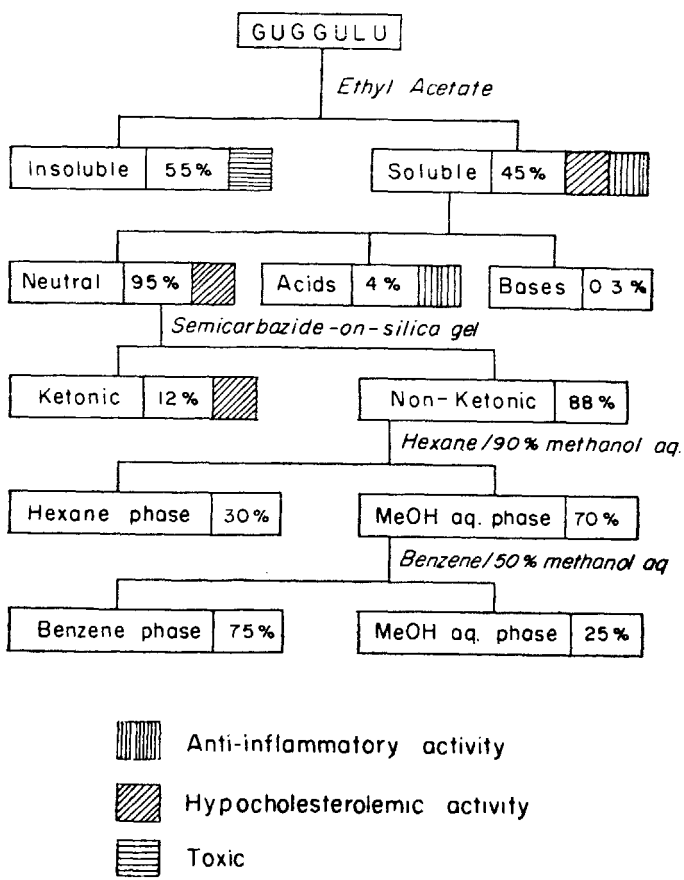
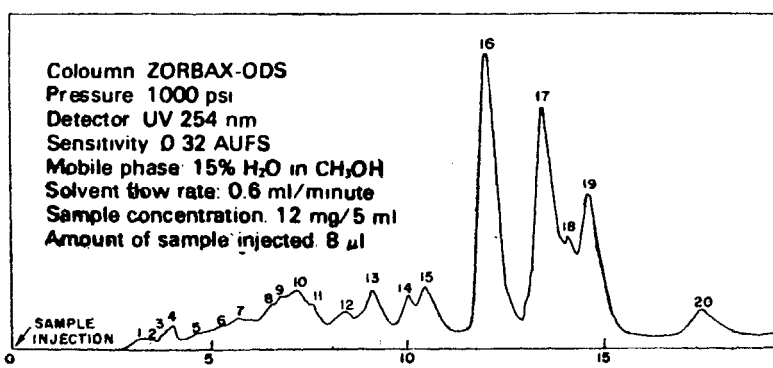


FIG 2 Segregation of *Guggulu.*

anti-inflammatory activity. It was soon found that the neutral portion contained several ketones, which had significant lipid-lowering activity. A simple method using semicarbazide-on-silica gel was developed[97] to effectively separate these ketones, which constituted ~ 12 per cent of the total neutral part. The non-ketonic portion was essentially devoid of any lipid-lowering activity.

Next phase of the research was aimed at separating the ketonic mixture into individual compounds and establishing which of these are responsible for the lipid-lowering activity. As judged from thin-layer-chromatography (TLC) and high-performance-liquid-chromatography (HPLC; Fig. 3), the ketonic fraction was quite complex. HPLC shows a minimum of twenty components. Actually, the number can be much more. That this indeed was so, became clear when we later learnt that HPLC peak 16 consisted of four compounds. By systematic column chromatography aided by TLC, we finally succeeded in isolating several pure compounds,[92a,94] including those responsible for lipid-lowering activity. We consider this a fortuitous achievement, as isolation of useful biologically active compounds from natural materials is often-than-not beset with many hurdles and imponderables. Structures of these compounds were established with the aid of modern spectral techniques coupled with degradative or synthetic work as found necessary. These structures are shown in Fig. 4. The approximate concentration, as ascertained by actual isolation of each of these ketones in the total gum-resin, is also given. From Fig. 3, it is clear that these compounds constitute ~60 per cent of the total ketone fraction. Compounds *11*, *12*, *13* have been known earlier. Compound *11*, now named *Z*-guggulsterol, had been known from synthesis, but was encountered in nature for the first time in *guggulu*. It is interesting to know



1–15 : unidentified
16 : *Z*-guggulsterol, (20S) -20-hydroxy-4-pregnen-3-one, guggulsterol-VI, *E*-guggulsterone
17 : *Z*-guggulsterone
18 : unidentified
19 : (20R)-20-hydroxy-4-pregnen-3-one
20 : guggulsterol-I

FIG 3 High-performance-liquid-chromatography of ketone fraction of *Guggulu*.

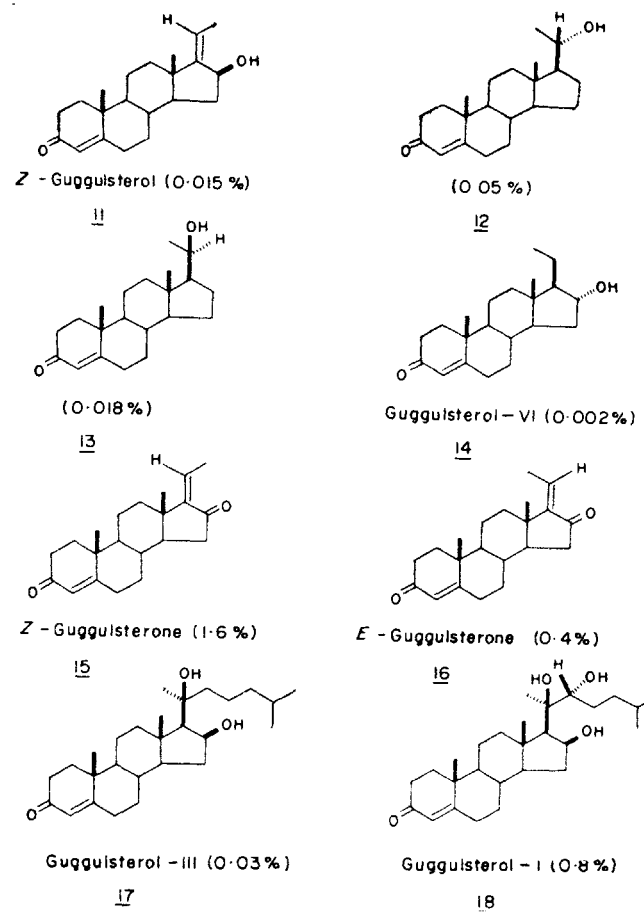


FIG 4 Ketones isolated from *Guggulu*

that the other two minor constituents (*12*, *13*) of the gum-resin have been reported earlier as components of defence secretions of certain water beetles. Thus, compound *12* is present in the defence secretion of *Acilius sulcatus*, while its 20-epimer (*13*) is elaborated by its cousin *Ilybius fenestratus*.[98]

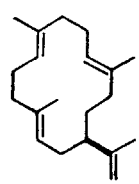
Compounds *15*, *16* which constitute some 2 per cent of the gum-resin are the major components of the ketonic fraction, and are responsible for the lipid-lowering activity of *guggulu*. These compounds, though isolated from nature for the first time, had been known synthetically much earlier.[99] As is the usual practice we have given these compounds the trivial names, Z-guggulsterone (*15*) and E-guggulsterone (*16*).

The remaining three ketones (*14*, *17*, *18*) are new compounds and their structures were confirmed by partial synthesis. Final stereochemical details for guggulsterol-I (*18*) were established by X-ray crystallography.[100]

The lipid-lowering activity of *Z*- and *E*-guggulsterones has been mentioned earlier. However, since the total ethyl acetate extract of gum resin has comparable activity, it follows that other constituents present in the ethyl acetate extract may be exerting a synergistic action on the biological activity of these compounds. In view of this, a detailed chemical analysis of other fractions (Fig. 2) was undertaken.

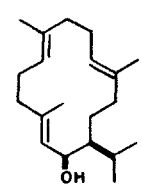
Other Constituents

The hexane phase material constitutes ~ 9 per cent of the gum-resin, and consists essentially of diterpenoids, besides a small percentage of chlosterol (*21*) and other unidentified compounds. The diterpenoids consist of a new diterpene hydrocarbon, cembrene-A (*19*); ~ 10 per cent), and its related alcohol, mukulol (*20*; ~ 40 per cent), besides other related minor terpenes, which appears to be artifacts.[92b,93,101] Cembrene-A is the simplest cembrenoid arising from 1,14-cyclization of geranyl-geranyl pyrophosphate, the biogenetic precursor of diterpenoids. Structure of this compound was arrived at by spectroscopic methods and confirmed by a chemical correlation with (+)-limonene. It is interesting to note that the trail-marker of Australian termites, *Nasutitermes exitiosus* has been shown to have the same structure.[102] When a modified procedure for separation was employed, another steroid, designated guggulsterol-II (*22*) could be isolated. Its structure was arrived at by spectral methods and confirmed by partial synthesis.[92a]



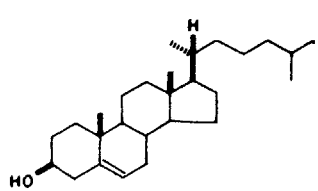
Cembrene -A

19



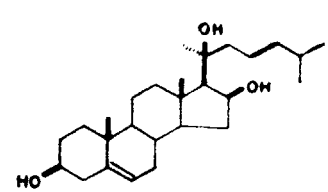
Mukulol

20



Cholesterol

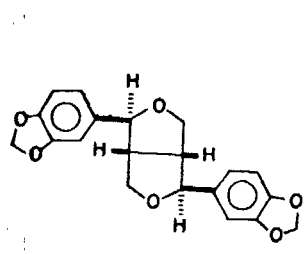
21



Guggulsterol - II

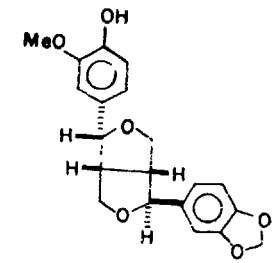
22

Material contained in the benzene phase (Fig. 2) constitutes ~ 14 per cent of gum-resin. Four lignans (*23–26*), of which two (*23, 24*) were known, have been isolated from this cut. The two new lignans, named guggullignan-I (*25*) and



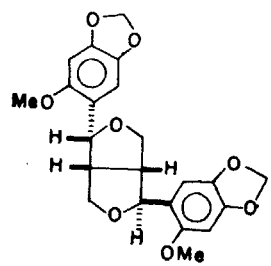
Sesamin

23



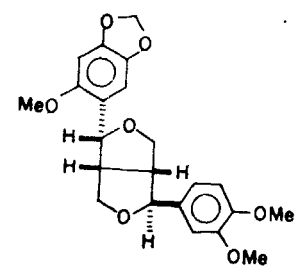
Pluviatilol

24



Guggullignan - I

25



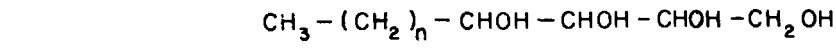
Guggullignan - II

26

guggullignan-II (*26*) were characterized by spectral methods.[103,104] A series of long-chain polyols esters were also isolated. These esters are derived from homologous polyols and ferulic acid. The polyols were recognized as tetrols of general structure *27* in which C_{20} and C_{18} compounds predominated. Configuration of these polyols has been established by synthesis starting with D-glyceraldehyde.[104,105] These polyols which have been given the generic name 'guggultetrol', have all been found to have the D-*xylo* configuration. Structure *28* is a typical representative of these compounds. This is the first report on the occurrence of such compounds in nature, and they appear to be important because of their structural similarity with the biologically important phytosphingosines (*29*). Phytosphingosines are present in cerebrosides and gangliosides.[106]

Gugulipid, a Modern Ayurvedic Drug

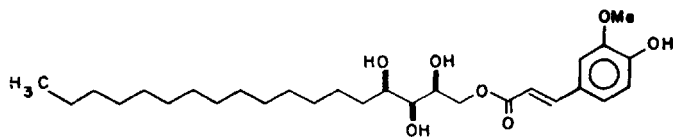
Quite early in the course of this work it was concluded, that instead of using pure *Z*- and *E*-guggulsterones for developing a hypocholesterolemic/hypolipemic drug, it will be better if a standardized ethyl acetate extract of *guggulu* is developed for clinical use. This decision was motivated, firstly, on purely commercial considerations so that the product will be economically viable and competitive, and secondly, because of the fact that other components of this ethyl acetate extract appear to have significant synergistic effect. Thus, detailed pharmacological and



$CH_3-(CH_2)_n-CHOH-CHOH-CHOH-CH_2OH$

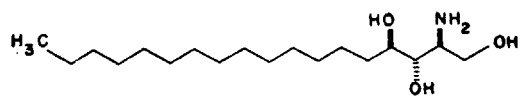
n = 13,15 (minor : n = 11,12,13,14,16,17)

27



D – *Xylo* – Guggultetrol - 18 ferulate

28



Phytosphingosine (C_{18})

29

toxicological studies and various phases of clinical trials have been conducted by CDRI on a standardized ethyl acetate extract (Fig. 2) of *guggulu*. This extract has been named 'gugulipid', and has been standardized to contain 4.0g of *Z*- and *E*-guggulsterones per 100g of the extract. Estimation of these standards is readily done by HPLC.

Detailed pharmacological studies have been conducted on rats, rabbits and monkeys. Thus, in normal rats oral administration of gugulipid at 100mg/kg body weight daily for 30 days led to serum cholesterol lowering by 34 per cent and of serum triglycerides by 26 per cent. The corresponding values for 100 mg/kg of clofibrate, a standard hypocholesterolemic drug, were 39 per cent and 30 per cent respectively. Fig. 5 depicts the effect of gugulipid in hyperlipidemic rats (high-fat diet), while Fig. 6 gives the results with hyperlipidemic monkeys; the treated monkeys showed 50 per cent and 30 per cent decrease in low-density and very low density lipoproteins respectively. In a similar study with hyperlipidemic rabbits (high-fat diet) oral ingestion of gugulipid at 50 mg/kg body weight daily for 8 weeks caused a fall in serum cholesterol by 40 per cent and triglycerides by 30 per cent.[107]

Gugulipid displays mild anti-inflammatory activity, no C.N.S. or diuretic activity. In mice the LD_{50} value was 1600mg/kg both oral or intraparenteral. Subacute and chronic toxicity studies were carried out in rats, dogs and monkeys; no

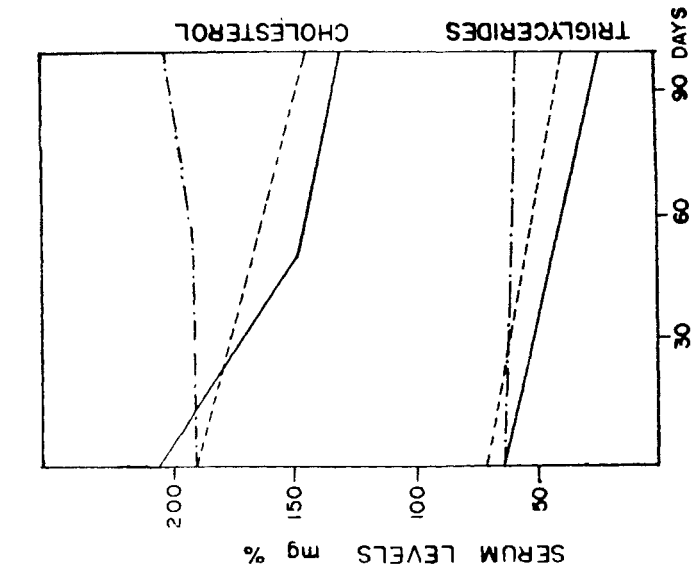


FIG 6 Gugulipid in hypolipidemic monkeys.

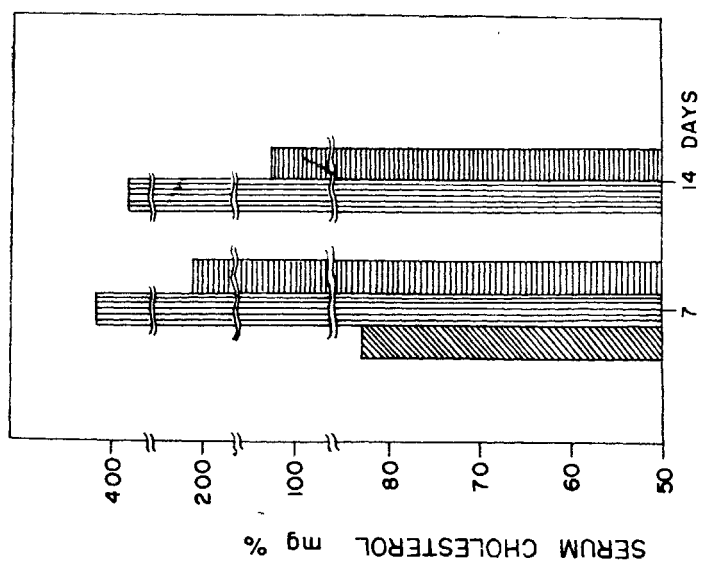


FIG 5 Gugulipid in hyperlipidemic rats.

adverse effects were noticed. Gugulipid was also shown to be devoid of any teratogenic or mutagenic effects.

Phase I, II and III clinical studies have been carried out on human volunteers. In Phase III, for example, a total of 87 hyperlipidemic patients, male and female, in the age-group 38–48 years participated. The studies were double-blind and were conducted in Bangalore, Bombay, Jaipur and Lucknow. The patients received 1500 mg/day of gugulipid or clofibrate in three divided doses for 12 weeks. The results showed that gugulipid is a safe and effective lipid-lowering agent comparable in efficacy to clofibrate, but with better compliance. Thus, for example, in Bangalore trials the mean reduction was 22 per cent and 14.5 respectively for cholesterol and triglycerides in case for gugulipid, while the corresponding figures for clofibrate were 18 per cent (cholesterol) 14 per cent (triglycerides). The average initial levels of cholesterol and triglycerides in the patients were 220mg per cent and 150mg per cent respectively.[107]

Gugulipid was cleared by Drug Controller (India) in June 1986 for marketing. It is now (Nov. 1987) being manufactured and marketed by CIPLA, Bombay.

SHATAVARI

I would also like to discuss briefly the results we have obtained with another Ayurvedic crude drug, *shatavari*. *Shatavari* of commerce comprises dried, decorticated roots of *Asparagus racemosus*.[62,108] Several therapeutic attributes have been claimed in the classical Ayurvedic literature. Fig. 7 shows two such quotations pertaining to its use in cases of threatened abortion and as a galactogogue.[109,110] Preliminary pharmacological screening of various extracts of the crude drug appeared to confirm these claims.[111-113]

शतावरी गुरुः शीता तिक्ता स्वाद्वी रसायनी।
मेधाग्नि स्निग्धा नेत्र्या गुल्मातिसारजित् ॥
शुक्रस्तन्यकरी बल्या वातपित्तास्रशोथजित्।
महाशतावरी मेध्या हृद्या वृष्या रसायनी ॥

(भावप्रकाश)

शतावरी सिद्ध घृत (पुंसवनं/गर्भदं)

(अ. हृदय उत्तरस्थान)

FIG 7 Sanskrit *Shlokas* giving medicinal attributes of *Shatavari*.

After considerable experimentation involving biological screening of various extracts for antioxytocin activity, scheme finally evolved for isolation of active fractions is shown in Fig. 8. At this stage it should be mentioned that Professor B B Gaitonde, who collaborated in this project considered specific antioxytocin activity (rat, guineapig, rabbit uteri) as a good indicator of anti-abortifacient activity. This separation scheme led to the isolation of a glycosidic fraction having specific antioxytocin activity. This material was found to be a complex mixture of at least nine compounds. Of these only one glycoside, named, Shatavarin-I, showed specific antioxytocic activity, both *in vitro* and *in vivo*; the compound showed no progestational or esterogenic activity.

Structure of Shatavarin-I (*31*) has now been worked out essentially on the basis of its spectral characteristics and enzymic hydrolysis to Shatavarin-IV(*30*).[114,115]

Thus, this study again turned out to be confirming ancient claims of Ayurveda.

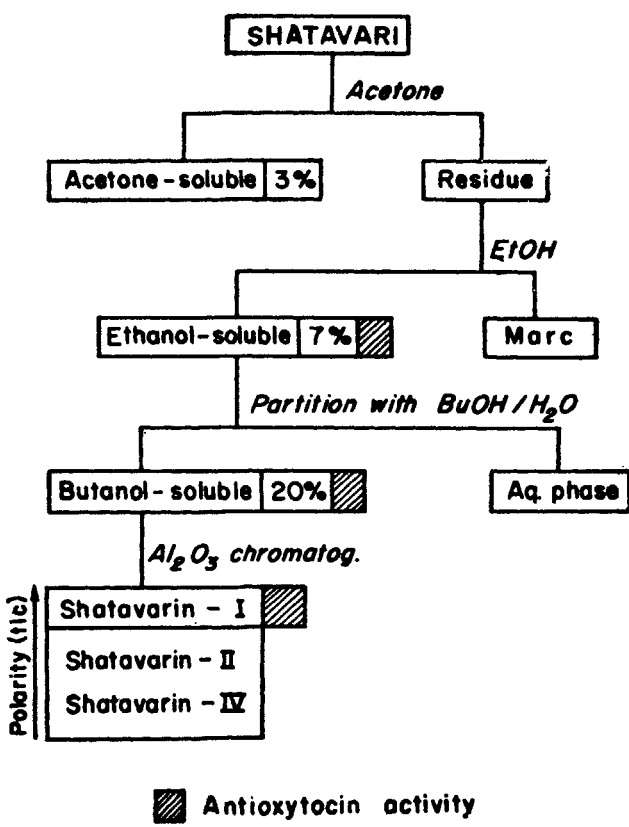
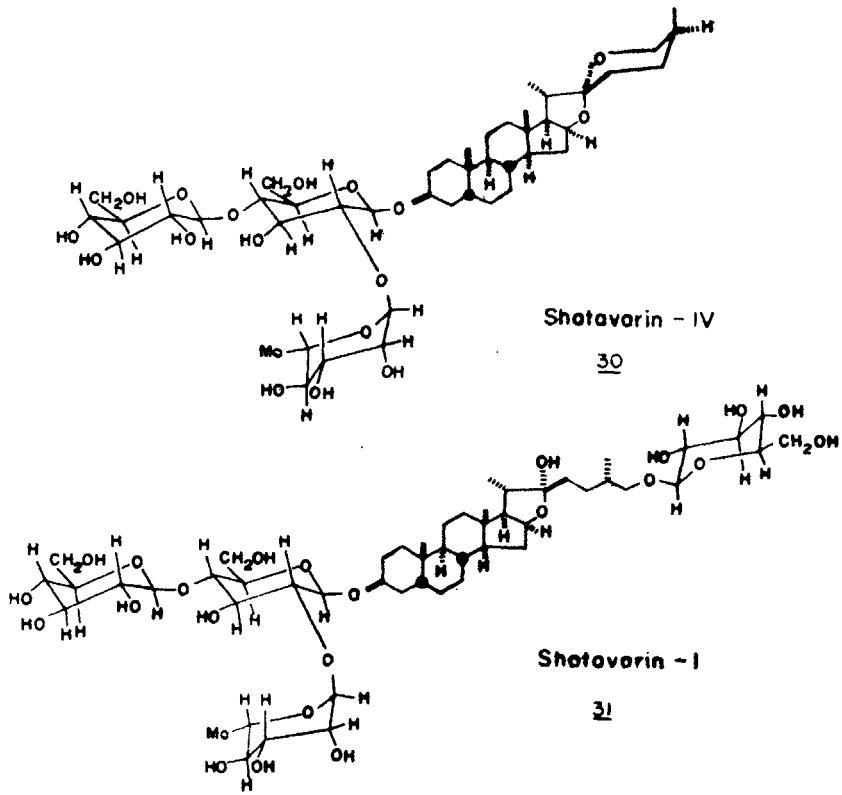


FIG 8 Scheme for the isolation of an active principle from *Shatavari*.



HARNESSING AYURVEDA FOR DRUG DEVELOPMENT

The material presented thus far puts Ayurvedic *materia medica,* as judged by modern parameters, in a reasonably acceptable position. Over the past two decades or so, a lot of data on the pharmacological, biological and therapeutical activity of many Ayurvedic single drugs, as well as compound preparations, have been published.[116] In any number of cases biological attributes of the Ayurvedic drugs appear to have been demonstrated. By way of illustration, some examples are given in Table VI. Even though, much of these data might not have been collected under ideal experimental conditions, a positive trend is more than evident. Considering all these, along with many as yet unexplored Ayurvedic drugs and folklore herbs, we have on hand a promising resource for development of useful drugs on modern lines. How does one go about achieving this ?

Before proceeding to answer the above question, one must tackle another one first, that is, if the Ayurvedic preparations are efficacious why not continue with these as such ? To my mind, the answer is simple. Modern science and technology have provided us with unique tools, which must be used to further refine these preparations. No system, no knowledge can afford to remain static. Last word

TABLE VI

Some ayurvedic crude drugs with pharmacologically/therapeutically proven claims

No.	Plant		Type of Activity
	(Botanical)	(Sanskrit)	
1	*Achyranthes aspera*	*Apamarga*	Diuretic[62,117]
2	*Acorus calamus*	*Vacha*	Tranquilizer[62]
3	*Adhatoda vasica*	*Vasa*	Bronchodilator, Oxytocic[118]
4	*Artemisia vulgaris*	*Nagadamani*	Cardiac tonic[50,62]
5	*Bacopa monnieri*	*Braahmi*	"Memory"[62,119,120]
6	*Boerhaavia diffusa*	*Punarnava*	Diuretic, Antiinflammatory[62,119,121]
7	*Butea frondosa*	*Palasha*	Anthelmintic[62,119,122]
8	*Cassia fistula*	*Aaragwadha*	Cathartic[62,110]
9	*Cedrus deodara*	*Devadaaru*	Spasmolytic[110,123]
10	*Celastrus paniculatus*	*Jyotishmati*	"Memory"[110]
11	*Centella asiatica*	*Mandukaparni*	"Intelligence"[62,119]
12	*Cissus quadrangularis*	*Vajravalli*	Healing of bone fractures[62,119]
13	*Curcuma longa*	*Haridraa*	Antiinflammatory[110,119,125]
14	*Eugenia jambolana*	*Jamboo*	Hypoglycemic[62]
15	*Holarrhena antidysenterica*	*Kutaja*	Antidysenteric[62,110,126]
16	*Picrorhiza kurroa*	*Katukaa*	Antihepatoxic[63,127]
17	*Pueraria tuberosa*	*Vidarikanda*	Galactagogue[110,128]
18	*Sida rhombifolia*	*Mahabala*	Anabolic[129]
19	*Swertia chirata*	*Kairata*	Febrifuge[110,130,131]
20	*Withania somnifera*	*Ashwagandha*	Anabolic[110,132,133]

on any subject can never be written. With expanding knowledge, horizons of perception widen, generating new, valid points of view, which must be met. Ayurveda itself provides an excellent example of steady development till the medieval period, when because of foreign onslaughts and political domination. Ayurveda became stagnant.[46,134] Thus, it is essential that Ayurvedic preparations get all the benefics of modern chemical, biological and pharmaceutical practices.

Now, returning to the first question of harnessing Ayurveda for modern drug development, a different approach than that normally adopted for drug discovery from plant sources is called for. Since the Ayurvedic formulations, as well as its crude drugs have been in use in this country and the neighbouring countries for many many centuries, it would not be unethical to evaluate these materials clinically first. I have propagated this view, which formed the core of the Composite Drug Research Scheme,[76] over the last many years.[3,74] This approach would also take care of the various imponderables, such as the question of right animal models, therapeutic action *via* prodrugs or by way of improving body functioning, or the question of synergism/antagonism. Such factors have often vitiated the outcome of drug discovery from natural sources. Efforts should be expended in two directions : (i) evaluation of therapeutic efficacy of standard Ayurvedic preparations and collecting sufficient scientific data to permit standardization, and

(ii) search for new biologically potent entities from Ayurvedic single drugs to permit later, development of a new drug as such or by providing a new model for development of a more effective synthetic analogue. Figs. 9 and 10, which are self-explanatory, depict the various stages which will have to be gone through in this effort.

In this suggested programme there are two crucial points which need elaboration. First is the selection of the target disease. In the final analysis, drug therapy is one. It is immaterial what the source of the drug is, so long as it is effective, safe and reasonably priced. Thus we should invest our time, effort and funds in those areas where Ayurvedic *materia medica* has something unique to offer. Hepatoprotective compounds, anti-ageing formulations, memory and intelligence enhancing products, compounds active against metabolic deseases,

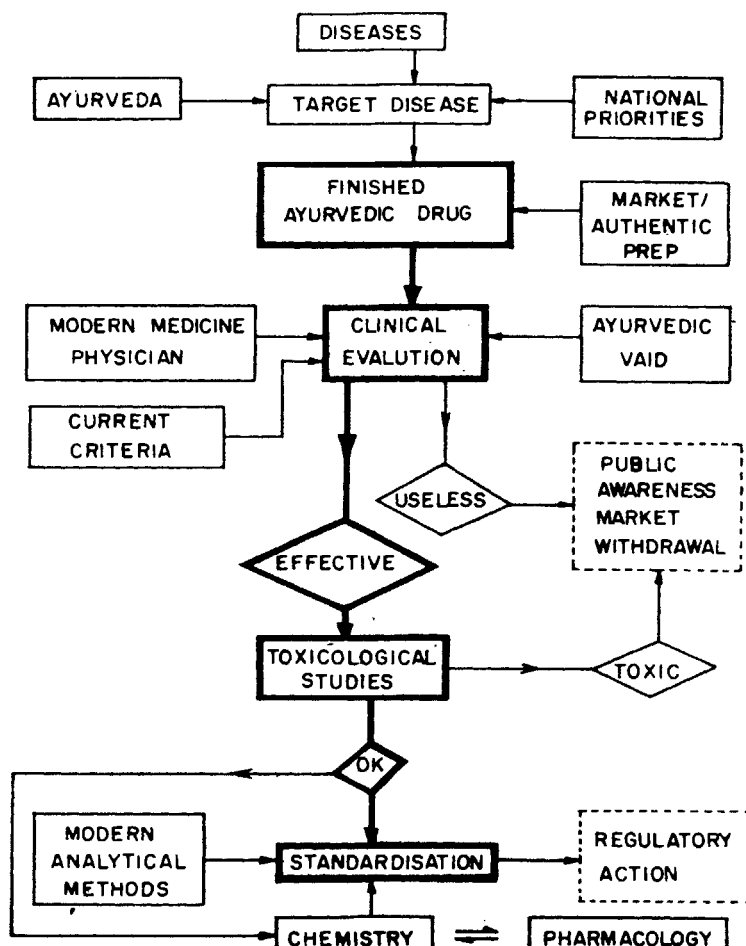


FIG 9 A plan for modern version of ayurvedic compound drugs.

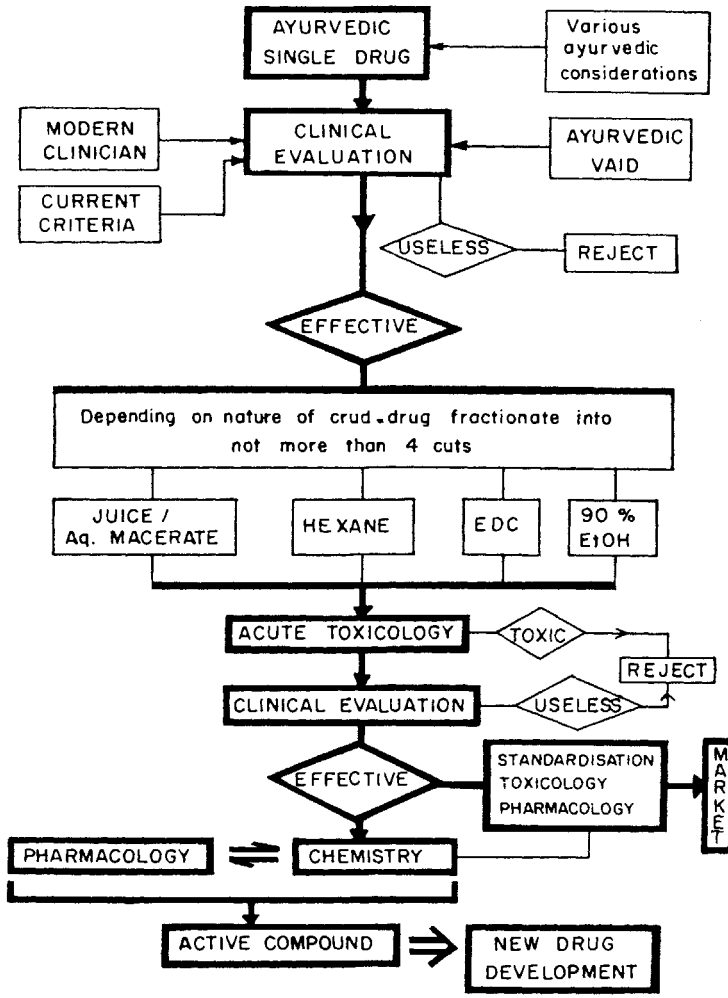


FIG 10 A plan for ayurveda-based modern drug discovery.

anabolics, antifertility compounds, rapid wound-healing products, immunopotentiators are some of the areas in which Ayurveda may have something worthwhile to offer. The second important point pertains to clinical evaluation of the drug. Both Ayurvedic and modern medicine physicians should be involved and should operate with full mutual understanding. The course of improvement in clinical manifestation of the condition should be judged using the latest criteria and standards. The objective would be to uncover something profound and not just a triviality.

In this endeavour, the usual factors associated with drug supply from natural sources will have to be tackled along scientific lines.

The final success of the programmes delineated in Figs. 9 and 10 will have to be measured in economic terms. A therapeutic breakthrough will remain sterile unless it is rewarded by economic success.

EPILOGUE

At the end, I wish to reemphasize the importance of Ayurveda in this part of the world and its potential in modern drug development. *Ayurveda* as we all know is still widely practiced in the Hindustan peninsula. The number of Ayurvedic practioners, both registered and otherwise, in India is estimated[134] to be 2,32,227. It is imperative that benefits of modern science flow to *Ayurveda* to make it once more vibrant and, pulsating with new activity. Ayurvedic *materia medica*, I believe, represents a treasure-trove waiting to be explored by all the modern techniques. Even with the present state of development in medicine, satisfactory therapy is available only for about the third of all ailments.[135] May be *Ayurveda* has something to offer ! Crores have been spent on the study of Indian medicinal plants and other formulations, but the outcome has been disappointing, chiefly because most of these studies were half-hearted, disjointed and ill-focussed. It is suggested that Government of India set up an effective modern facility dedicated to research in Ayurveda so as to enable it to effectively intermesh with modern medicine. After all, in the ultimate analysis, there cannot be different versions of the some science.

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