HISTORY OF NATURAL PRODUCTS CHEMISTRY IN INDIA

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Abstract

The flora of India is one of the richest of the world due to a wide range of climate, topology and environments in the country. There are more than 3000 officially documented plants in India that hold great medicinal potential. A large number of promising leads have come out of empirical investigation of natural products which have been incorporated in the Ayurvedic system of medicine which are being investigated along modern lines. More importantly, an enormous volume of studies has been carried out on them which has resulted in numerous new constituents, alkaloids, oxygen heterocycles, terpenes etc. being isolated and their structures elucidated. Several schools of natural products chemistry flourished and generations of gifted students have been trained.

Around the 1920s Simonsen established a tradition of research in terpenes first in Presidency college, Madras and then at IISC, Bangalore and authored a series of standard monographs on the subject. Siddiqui and Chopra injected earnestness into the study of natural products, the former concentrating on isolations and the latter on identifying biological activity in plant extracts. Natural products chemistry received an immense boost in India after the return of UK trained scientists, Seshadri and Venkataraman to take up positions in Delhi University and UDCT, Bombay respectively. While these two largely specialized in oxygen heterocycles, Banerjee who had received postdoctoral training in USA created a good school in synthetic steroidal chemistry at IISC, Bangalore. Natural products research gained further momentum due to the prodigious and productive efforts of Govindachari (Presidency College, Madras, Ciba, Bombay), Bhattacharyya (NCL, Pune, IIT, Bombay), Sukh Dev (NCL, Pune, Maltichem Research Centre, Baroda) and Asima Chatterjee (University of Calcutta). Active schools of research started also functioning in Pune University, Regional Research Laboratory, Jammu, Central Drug Research Institute, Indian Institute of Chemical Biology etc. Interest in natural products chemistry sustained for some more years through the efforts of the next generation of researchers but has gradually waned mainly due to changing fashions in organic chemical research. Work during several decades was related to isolation, structure determination and occasionally total or partial synthesis, often accompanied by biological investigation. Total synthesis of complex natural products, not necessarily of Indian origin, has been achieved in India in quite a few laboratories, notably by Mehta (IIT, Kanpur, University of Hyderabad, IISc, Bangalore). Rather uniquely biosynthetic studies using radiolabelled substrates have been carried out by Bhakuni and Kapil (CDRI, Lucknow) as part of a broad programme on the investigation of Indian Medicinal Plants. Pathway engineering or chemical biology, an emerging area of considerable practical utility is being carried out at IIIM. Results are awaited.

“Marine Natural Products” is a segment of great importance and have been the subject of intense, global investigation. However it has not attracted the attention it deserves from our scientists barring a few stray enthusiasts. Public Agencies like DBT, DST and CSIR have been funding ambitious programmes for exploiting our bio-resources. In view of the importance of natural products chemistry from the point of view of basic science as well potential beneficial applications, efforts are urgently needed for its revitalization.

Key words: Alkaloids, Biological activity, Chemical investigation, Historical survey, Oxygen heterocycles, Terpenes, Terrestrial and marine Indian flora.

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1. INTRODUCTION

Natural products have been intimately connected with human civilization from time immemorial. The term ‘natural products’ may refer to both inorganic and organic compounds but the focus of the review is the latter. Natural products chemistry has attracted the attention of organic chemists over the ages for several well known reasons: basic interest in organic chemical structures of immense diversity found in nature; pushing the frontiers of organic chemistry; discovery of many novel degradative and synthetic methods; development of many theoretical concepts, e.g. conformational analysis; commercial value in many different fields such as dyes (indigo), flavours, fragrances, edible oils; and particularly in the area of therapies for diseases, e.g. reserpine, quinine, camptothecin, vincristine, taxol and crop protection (neem constituents) which have also inspired elaboration by semisynthesis of near or distant analogues.

For obvious reasons research in natural products chemistry is relevant and appropriate for Indian scientists, India reportedly having 8% of the world’s biodiversity. India is a vast country with varying agriclimates, tropical and subtropical, manifested in a profusion of plant life, numbering over 45,000, several being unique to the country. Many plants have been used for several centuries for illnesses and wellness, in the Ayurvedic and other indigenous systems. In fact it is claimed that there are 3000 officially documented ones with good medicinal potential. While the applications of plant extracts alone or as a mixture have been documented in Ayurveda, efforts to identify their constituents seem to have started in the country only after the dawn of the twentieth century. From small beginnings around 1910, plant product chemistry grew rapidly in the following decades but has tapered off now. Marine resources also are valuable repositories of natural products. Indian coast line of 7516 km offers a great potential for finding secondary metabolites of complexity and utility. Whereas natural product chemists abroad had started exploring this source earlier, serious Indian efforts started in 1978 as a result of collaboration between Central Drug Research Research Institute and National Institute of Oceanography.

2. FOCUS OF THE ARTICLE

Natural products chemistry, as is well known, has as its important components, isolation, structure elucidation and synthesis. This article will focus on the historical contributions in terms of new molecules isolated in India whose structures were determined and some of which were synthesized. It will not touch such synthesis or efforts wherein natural products isolated elsewhere have been targets for synthesis despite the fact that there have been a significant number of Indian chemists who have been engaged in the endeavour and a few gifted chemists have been spectacularly successful in leaving an imprint in national and international fora.

A succinct appraisal of Indian laboratories to the chemistry of plant products has been given by T.R. Govindachari. This article will update it and survey marine natural products while also touching upon the general scenario of institutions and facilities.

2.1 Facilities for natural products research over the years

Extraction and isolation of natural products have been generally on conventional lines graduating from fractional crystallization to column chromatography and then to preparative HPLC but a few institutions have now advanced facilities like the one for extraction with solid carbon dioxide and LC-MS instrumentation capable of dereplication to identify known molecules and help assign structures of new molecules. The June 2014, Vol 31 issue of NPR (Natural Product Reports), devoted exclusively to use of mass spectrometry in natural products
research offers valuable information to Indian practitioners. Structures were determined in the earlier years by classical, laborious degradation studies and occasionally confirmed by synthesis. UV and IR started to be used in the 1950s. The advent of progressively more sophisticated NMR and mass spectral techniques in the West started trickling slowly into India from 1960 onwards with a few lucky institutions being able to possess them. The ultimate tool of structure proof came to be accepted as single crystal X-ray studies and was available very sparingly initially. In the last two decades due to generous funding from different government agencies, a profusion of latest instrumentations for NMR, Mass and X-ray have been installed in many laboratories. Regional instrumentation centres have made these facilities available to interested researchers in less fortunate circumstances. Over the years, using whatever facilities were available at that time Indian researchers have isolated many new compounds which were the first in the class with unique structures.

2.2 Facilitators of natural products research and years of their inception

Council of Scientific & Industrial Research (own laboratories and extramural grants) 1942; University Grants commission (through funding for centres for advanced studies and special assistance programmes) 1948, Indian Council of Medical research (intramurally as well as extramural funding for research in investigation of Indian Medicinal Plants) 1949; Department of Science & Technology (intramural research and extramural funding) 1971; Department of Ocean Development, Ministry of Earth Sciences (a small number of own institutions and funding of others for marine products research) 1982; Department of Biotechnology (the latest entrant with abundant funds for own Institutions as well as for external grants) 1990 were the major facilitators for studies and research products chemistry.

It should be noted that such funding is also available for a large number of junior and senior scholarships for doctoral and postdoctoral students. The monetary value of these fellowships has been happily adjusted for inflation to a reasonable extent over the decades.

3. Beginnings of Natural Products Chemistry in India

3.1 J.L. Simonsen

From data available in the literature, research in this area was initiated by J.L. Simonsen who taught at Presidency College, Madras during 1910-1918. He moved later to the Indian Institute of Science, Bangalore. He left India in 1928. His area of specialization was terpenoids and he is well-known for authoring several volumes of monographs on The Terpenes. His extensive research was substantially carried out at Presidency College and also from Forest Research Institute, Dehradun and is exemplified by isolation of longifolene I and identification of 3-carene as a major constituent of Indian turpentine.
He was one of the scientists responsible for starting the Indian Science Congress in 1914. It is interesting to note that he gave a talk in 1917 on a survey of the present stage of chemical research in India.

In spite of his contributions to sowing the seeds of natural products research in India, it appears that he did not create a school of research.

### 3.2 Ramnath Chopra

Indian interest in natural products chemistry has been rightly stimulated by knowledge of their medicinal uses. Ramnath Chopra working at School of Tropical Medicine in Calcutta between 1921 and 1941 and later at Calcutta Medical College has done pioneering work in this area. He laid emphasis on Indian indigenous drugs and their chemical composition and active principles. He investigated scores of medicinal plants such as *Alangium lamarckii*, *Psoralea corylifolia* and *Rauwolfia serpentina* and showed that the alkaloidal extract of the last plant elicited in animals, central depressant properties and lowered their blood pressure. This was picked up by Siddiqui and Vakil (see later). Chopra is known for his *Glossary of Indian Medicinal Plants* and supplement brought out by Council of Scientific and Industrial Research, India (CSIR). His work was undoubtedly an inspiration to later researchers, particularly so in Calcutta, to investigate Indian medicinal plants with a heritage of medicinal activity on modern scientific lines.

### 3.3 B.B. Dey

B.B. Dey who worked at Presidency College, Madras (1920-1944) after Simonsen, continued the tradition of research and made notable contributions in the field of plant products – isolation of thevetin from *Thevetia nerifolia*, heydotine from *Heydatis curcularia* and tandemlinine and todolalolac tone from *Toddaea aculeate*. He played an important role in inspiring quite a few students to take up natural products research. Noteworthy among the students he mentored were T.R. Seshadri and K. Venkataraman who worked for their M.A. degree in the early 1920s and proceeded to earn their doctorates under Robert Robinson in UK. They were followed several years later by T.R. Govindachari who got his M.Sc and Ph.D degrees from him (1937-1946) and augmented his knowledge and skills by joining as a postdoctor, Roger Adams, a leading luminary in Organic chemistry at the University of Illinois. Dey also worked on the development of electrolytic processes for imported dyestuffs as a war time necessity.

### 3.4 P.C. Guha

who joined the Indian Institute of Science in 1935 several years after Simonsen had left was actively engaged in the chemistry of essential oils and other natural products and inspired many students among which were two who shaped up as leaders in that area of chemistry, S.C. Bhattacharyya (I ISc Ph.D. 1944) and Sukh Dev (IISC Ph.D. 1950).

### 3.5 P.K. Bose

had significant achievements in the field of phytochemistry and synthetic organic chemistry at the University of Calcutta and then Bose Institute (total period 1930-1950.) He was responsible for mentoring many students, the most notable among them being Asima Chatterjee who earned her D.Sc degree with him (1944).

### 3.6 Salimuzzman Siddiqui

was another pioneer in chemical investigation of Indian plants who started working at the Tibbs College of Unani
workers for several years until it was isolated and studied by Morgan et al. in 1968.

4. Golden Age of Natural Products Chemistry

4.1 T.R. Seshadri who returned to India after doctoral work with Robert Robinson in UK, the undisputed leader in natural products chemistry at that time, started his professional career as professor of chemistry in Andhra University, Waltair (1937-1949) and later moved to Delhi in 1927. Later he moved to the Board of Scientific and Industrial Research in Delhi (1940-1951). He left for Pakistan in the aftermath of partition. He had a prolific output (considering the times) in isolating many plant products in a pure state. Among these may be mentioned the alkaloids ajmaline, ajmalinine and ajmalicine from the reputed *Rauwolfia serpentina* (1931), connessine 2, conessinine and conessidine from *Holarrhena antidysentrica* (1932) and nimbin, nimbinin and nimbidin from *Azadirachta indica* (1942).

He is particularly known for collaborating with Vakil in establishing the antihypertensive activity of *Rauwolfia* extracts in human clinical trials. However it is regrettable that he and other Indian researchers missed isolating the active principle, reserpine which happened at Ciba, Basel in 1952. Similar has been the case with *Azadirachta indica* where the active antidfeedant principle, azadirachtin A was missed by Indian University to head the Chemistry Department and after retirement, worked at the University’s Centre for Advanced study for Chemistry of Natural Products until his death in 1975. He attracted a large number of students to the departments (150 Ph.Ds) and established vibrant schools of research in both institutions. Many of his students became leaders on their own later. The prolific output of 1200 publications earned him enormous respect and admiration in India and significant reputation abroad. His major contributions were in the area of oxygen heterocycles. He was attracted to floral and animal colours. His group isolated and established structures of flavones, isoflavones and anthocyanins. His work on gossypol, the pigment from cotton seed oil served to clear up structural confusions. The elucidation of structure of santalin A from *Pterocarpus santalinus* Linn is worth mentioning. Gossytrin 3 from Hibiscus flowers and cyanomaclaurin 4 are cited as examples of his prodigious output which involved occasionally some other types of plant secondary
benzyloxyacetophenones to flavones. The reaction was independently discovered by Baker around the same time and has come to be known as Baker – Venkataraman Transformation. Venkataraman moved to University Department of Technology, Bombay initially as Reader in dyeing and printing and later as Professor and Head (1934-1957). He became the first Indian Director of National Chemical Laboratory (NCL), one of the several national institutions created by CSIR under the visionary leadership of S.S. Bhatnagar. Venkataraman retired from directorship in 1966 but worked there as emeritus scientist till his death in 1981.

Apart from isolation and structure elucidation, Seshadri carried out pioneering work on synthesis of oxygen heterocycles and synthetic methods such as selective O-methylation and demethylation, C-methylation etc. The Robinson connection was evident in his outlining a biogenetic pathway for the neoflavanoids (4-arylchromenes). Together with S.Rangaswami he also wrote a book on Chemistry of Vitamins and Hormones (1946 and 1952). Interested readers may consult an article with bibliography by Rangaswami⁴.

4.2 K. Venkataraman returned to India after his doctoral training with Robinson and started his research career rather modestly at Foreman Christian College, Lahore in the pre-partition years. He soon attracted the attention of organic chemists by announcing the conversion of O-

Influenced perhaps by the mission of UDCT to carry out research to help Indian industry and his duty as Reader in dyeing, Venkataraman got interested in the chemistry of dyestuffs which was important for the Indian dyes industry. He wrote the first two volumes of Chemistry of Synthetic Dyes and edited six more volumes during 1971-1978. These eight volumes along with the Analytical Chemistry of Synthetic Dyes earned him international acclaim and are standard monographs in this field till date.

Apart from this hobby, if one can call it so, Venkataraman made significant contributions in isolation and structural elucidation of naturally occurring flavones, isoflavones and naphthoquinones and to Lac pigments containing nitrogenous anthraquinone and anthraquinonoid insect pigments (kermesic acid) ¹. Cyclointegrin 5 from Artocarpus integer and morellin 6 from
personally involved with a group of ten scientists in natural products research. His interests were not confined to any single class of natural products but covered quite a few – alkaloids e.g. tylophorine 7 (the first phenanthraindolizidine alkaloid), echitamine, tiliacorine 8 (a bisbenzylisoquinoline with unique diphenyl link), kopsine 9 (a heptacyclic indole alkaloid, with H. Schmid, Zurich), ancistrocladine 10 (the first naphthylisoquinoline alkaloid from nature, of polyketide origin), 9-methoxycamptothecin; terpenes e.g. ishwarone 11, cedrelone, litsomentol 12; oxygen heterocycles e.g. wedelolactone 13. To the work carried out at Ciba, Drs. B.S. Joshi, P.C. Parthasarathy and N. Viswanathan contributed.

Garcinia morella are a couple of structures illustrative of his work with Ph.D students (85 in all) which resulted in 201 publications. Many of the students continued the tradition of their mentor. An article by Nitya Anand has full details of his work.5

4.3 T.R. Govindachari returned to India in 1950 after a productive postdoctoral stint with Roger Adams in US, joined the chemistry department of Presidency College, Madras as Professor and soon established a flourishing school of natural products chemistry concentrating mainly but not exclusively on plants with medicinal activity. The tempo of his activity continued unabated even after he moved in 1963 to head the newly established Ciba Research Centre in Bombay where he was
crystals of azadirachtin A and also several congeners.

Govindachari trained 25 Ph. D students, quite a few of them becoming illustrious scientists of acclaim in later years. His publications including chapters in several monographs on natural products number over three hundred and fifty. Out of these one has been already cited. Another one with the title ‘Five decades in the study of natural products’ illustrates the breadth, depth and passion he had for his chosen field. Full details of his career and contributions are available in an article by Nagarajan. Another article by Nagarajan gives brief but adequate information on the methodology of structure determination T.R.G’s group employed over the years, illustrated in the cases of representative molecules from different classes, alkaloids, and oxygen heterocycle and how continuously evolving spectral techniques were marshalled for this exercise over the years. This applies equally well for all the work of other natural products researchers in India.

4.4 Asima Chatterjee, after working with P.K. Bose, had further postdoctoral experience with L. Zechmeister at Caltech in USA and Paul Karrer in Switzerland. After her return in 1950 and a stint at Lady Brabourne College, she started on an illustrious career in natural products research as Reader in the department of chemistry, University of Calcutta in 1954, became professor in 1969 and after retirement in 1979, project coordinator for significantly. For a little over two decades, in the last part of his career, after retirement from Ciba, Govindachari continued his researches on natural products at Amruthanjan Research Centre (1977-1986) and Spic Agrochemical Research Centre (1987-2000) both in Madras, devoting much of his attention to the constituents of neem (Azadirachta indica) isolating the first ever
Centre for Advanced studies in the same department. Along with numerous gifted students, she worked on the chemistry of natural products from Indian medicinal plants and made important contributions in diverse classes of natural products like alkaloids, polyphenolics and terpenoids. She is particularly reputed for her work on the chemistry of indole alkaloids wherein her original contributions were many and manifold. Worthy of mention are: alkaloids of Rauwolfia, Vinca, Alstonia (21 alkaloids from A. vanenata), Rhazya; structures of rauwoliscine, ajmaline. Venoterpene and grandifoline are some more examples chosen at random. Chatterjee also carried out synthetic studies on a number of complex indole, quinoline and isoquinoline alkaloids through novel routes.

Chatterjee was always attached to the applications of natural products as evidenced by the development of Ayush 56, a combination of marsilin, a sedative-anticonvulsant from water fern (Marsilea minuta) mixed with jatamansi (Nardostachys jatamansi). Chatterjee published prolifically (369 papers and a Treatise on Indian Medicinal Plants in 6 volumes for CSIR) and also had the distinction of serving the country as MP for Rajya Sabha. Julie Banerjee, her daughter who has carried on her tradition, has contributed a definitive article on her.

4.5 S.C. Bhattacharyya, after his early Ph.D. work at IISc, Bangalore earned another Ph.D degree in Cambridge working with B. Lythgoe on natural products. After returning to India in 1949 and a short stint at IISC, he joined National Chemical Laboratory, Pune and started a very productive phase of extensive and in-depth investigation of Indian plants. The research interests were pursued when he moved over to Indian Institute of Technology, Bombay in 1966 and after retirement in 1978 to Bose Institute,
Calcutta which he left in 1984. His large group was involved in isolation, characterization and structure determination of the fragrant principles of essential oils such as those from vetiver, sandalwood, costus root and agarwood. One of his seminal contributions was the demonstration of the antipodal nature of constituents of vetiver oil – North Indian variety levorotatory, from other origins, dextrorotatory including the cultivated south indian variety. Over the years, together with ninety three doctoral students, he reported the isolation of over a hundred natural products, especially terpenoids like agarospiral and khusiol and several furo and pyranocoumarins. Additionally he is also widely recognized for the synthesis of various macrocyclic ketones from indigenous commercial raw materials and complex coumarins of the visadine group and secondary metabolites of Jatamansi with vasodilatory properties. Over two hundred scientific publications stand testimony to his research output as mentioned by Trivedi, Contractor and Ghosh in an article.

4.6 Sukh Dev, another natural products chemist of great repute, after earning his Ph.D from IISC in 1950, started an independent scientific career in the same place working on certain woods, oleoresins and essential oils which formed a rich collection in the chemistry department. He left IISc at the end of 1959 with a D.Sc degree and moved to the National Chemical Laboratory with better facilities for elucidation of complex structures. Together with a large group of students and co-workers, he soon initiated a vigorous school of research in terpenes and maintained the tempo when he left NCL in 1974 to establish a private institute, Maltichem Research Centre in Baroda for an industrial house. It is interesting to note that his tenure at NCL overlapped with that of Bhattacharyya during 1960-1966. One wonders what the effect of competing fragrances of essential oils would have been on the ambience of NCL!

In 1988 Sukh Dev moved from Maltichem to the chemistry department of Indian Institute of Technology, Delhi and after a five year stay there in 1993 to B.R. Ambedkar Centre of Delhi University.

Sukh Dev and his group are responsible for the isolation, chemical studies and absolute stereostructures of many terpenes such as zerumbone, longicyclene, himachalenes, Lac constitutuets, malabaricol and kodocytochalasins. Many represent new fundamental types and are considered “classics” – longicyclene, atiserine, cheilanthatriol. Sukh Dev studied acid induced transformations of longifolene to isolongifolene, investigated the commercial values of natural products such as himachalene and very importantly ‘restructured’
widely available natural products into chiral molecules of economic value e.g. 3-carene to (-) menthol and pyrethroid (insecticides) intermediates. During these years Sukh Dev also got interested in a big way into chemical investigation of Ayurvedic crude drugs in association with Central Drug Research Institute. The association was fruitful as exemplified by the isolation and confirmation of activities of guggul sterones \(^{23}\) (E, Z mixture, Z isomer shown) from guggul, the resin exudate from *Commiphora mukul* with antihyperlipidemic activity. His passion and dedication to this exercise live on as evidenced by his book, *Prime Ayurvedic Plant Drugs – A Modern Scientific Appraisal*, the second, enlarged addition of which has been published in 2012. Sukh Dev mentored ninety two Ph.D students and published over three hundred and seventy five research papers and also the Handbook of Terpenoids, CRC Press, 1982. More information is available in the article by Vishwakarma Singh and A. Srikrishna.\(^{12}\)

5. **Natural Products Research in India (contd) – A Tour of Various Centres**

The narrative so far referred to the contributions of some leading researchers whose work had been nationally relevant and acclaimed internationally. There have been very many groups all over the country where research on natural products chemistry has been carried out. A good number of these have been engaged in investigating extracts of medicinally important plants and testing them for various biological activities (often in medical or pharmacy colleges) and also isolating a large number of known compounds and occasionally some new ones. This article does not claim exhaustive coverage but focuses on institutions where there have been significant and continuous engagements of a high standard. Readers are invited to participate in the tour.

5.1 **Indian Institute of Integrative Medicine (formerly Regional Research laboratory), Jammu**

IIIM, belonging to the chain of national laboratories created by CSIR, from its inception in 1941 had carried out natural products research of a high standard on the chemistry and biological activity of medicinal plants. Later on they started studying marine products also. Some high lights are presented.

**C.K. Atal** had a very strong pharmacognosy background. His group isolated boswellic acids from *Boswellia serrata* with anti-inflammatory and analgesic activities – several preparations in the market have standardised extracts. Among other exercises can be mentioned his work on the genus *Crotalaria* from which pyrrolizidine alkaloids were isolated e.g. cromadurine \(^{24}\) with a macrocyclic lactone unit\(^1\). Among his contributions the most important
would perhaps be research on piperine as a bioavailability enhancer for drugs, e.g. rifampicin,\textsuperscript{13} a theme picked up by Quazi later.\textsuperscript{14} The bioenhancing effect of piperine was attributed to both suppression of metabolic degradation by enzymes and inhibition of reflux pump (PgP).

**K.K. Bhutani** – chemical investigation, isolation, structure elucidation, biological studies e.g. Tylophora alkaloids, neem constituents (work pursued further at National Institute of Pharmaceutical Education & Research (NIPER), Mohali (see later).

**R.S. Kapil** – Furanoditerpene glycosides from *Tinospora cordifolia* with immunostimulant and hepatoprotective activities; synthesis of natural products including carbazole alkaloids from the curry plant, *Murraya koenigii* (see further under CDRI).

**Ram Vishwakarma** – extensive work on natural products, isolation and synthesis e.g. dysoline \textsuperscript{25}, anticancer alkaloid, a new regio isomer of rohitukine, from *Dysoxylum binectariferum*\textsuperscript{15}.

A significant achievement of IIIM in the last few years has been the culmination of development of risorine, a combination of rifampicin with the bioenhancer, piperine for the treatment of tuberculosis. In collaboration with Cadila Pharma, risorine has undergone successful clinical trials in India and obtained regulatory approval in late 2009.\textsuperscript{16} The combination is in the Indian market.

An important and significant objective of IIIM is to work on pathway engineering and systems biology approach towards homologous and heterologous expression of high value phytochemicals e.g. the antimalarial artemisinin and picrosides with hepatoprotective properties. The realization of these objectives will have profound significance.

### 5.2 Delhi University

The contributions of T.R. Seshadri have been already described.

**S. Rangaswami** had a thriving school of research in Andhra University to begin with (1949-1963) and later in Delhi University (1963-1977). He was closely attached to Seshadri. His interest was chemistry of natural products esp with biological activity including heart poisons and drugs, plant drugs used in the Ayurvedic and Siddha systems, ferns and wood rotting fungi. His major discovery was peruvoside \textsuperscript{26}, a cardiotonic glycoside from *Thevetia nerifolia* which ranks with three best drugs in cardiac therapy, viz digoxin, digitoxin and oubain. It has been
marketed in Europe as encordin. His book on Chemistry of Vitamins and Hormones with Seshadri has been referred to already.

A.C. Jain who had been mentored by Seshadri came to Delhi University in 1979 after productive research outputs in Jammu and Himachal Pradesh Universities. In addition to his major interest in new general methods of synthesis of oxygen heterocycles and other systems, including biomimetic methods, he isolated many new natural products, e.g. pyranoisoflavone, corylin 27 from Psoralea corylifolia and triterpene, putranjivic acid 28 from Putranjiva roxburghii.

Harkishan Singh reported the isolation of diabolin (Wieland-Gummlich aldehyde) from Strychnos potatrum and erythrotisine from Erythrina suberosa seeds.

5.4 National Institute of Pharmaceutical Educational Research (NIPER), Mohali

K.K. Bhutani moved to this institute some years ago from IIIM. He has an active group doing isolation, structure determination and biological testing. He has brought out a useful compendium “Chemical profiles – data bases of Ayurvedic plants derived from single and poly herbal preparations, HPTLC etc.” NIPER has been organizing regular conferences on Drug Discovery from Natural Products and Traditional Medicines of India. Bhutani’s article with V.M. Gohil in this area is an important and useful contribution which lists all the herbal preparations sold in India but also reveals, rather sadly, that so far no single molecule has been isolated in India by Indian researchers which has become a drug.

5.5 Banaras Hindu University

S. Ghosal who had been mentored by Asima Chatterjee, was involved passionately in Pharmaceutical Chemistry research, defining the true nature and characterization of key natural drugs esp. of Ayurveda e.g. Shilajit (antidiabetic), a thick sticky, tar-like substance with a colour ranging from white to dark brown, some times found in the Himalayas, aśvagandha, āmla etc. He has carried out chemical work on plants like Sida cordifolia and has over three hundred and fifty publications and an authoritative monograph on Shilajit.

5.6 Central Drug Research Institute, Lucknow

Right from its inception in 1951 CDRI has had a major engagement in the chemical
investigation of Indian medicinal plants. Some high lights are:

M.M. Dhar, R.P. Rastogi, B.N. Dhawan and others carried out detailed studies on standard extracts of medicinal plants of India for a wide spectrum of biological activities – antibacterial, antiprotozoal, antiviral, anticancer and hyperglycemia in a wide range of pharmacological systems which have appeared as a series of publications. Ciba, Bombay had done a similar investigation in their natural products group.

**M.M. Dhar** and group isolated the diterpene, coleonol from *Coleus forskolii briq.*, a plant known in Ayurveda to treat heart conditions. This had good antihypertensive and positive inotropic properties. Hoechst Research Centre, Bombay isolated the same product simultaneously and named it forskolin. Structure 29 was derived by degradation and spectral studies, finally by X-Ray. Merck Index has named the molecule as “colforsin”. The insoluble molecule has been solubilized as a cyclodextrin complex by Sami Laboratories, Bangalore and approved in India for the treatment of glaucoma.

![Forskolin](image1.png)

**R.P. Rastogi** from the group of S.Siddiqui was involved in the isolation of the active principle, kutkin of *Picrorhiza kurroa*, with hepatoprotective properties, bacosides from *Bacopa monnieri*, known for its memory enhancing properties and the anticancer germacrolide, tagitin F 30 from *Tithonia tagetiflora* Dept. Rastogi has contributed a useful Compendium of Indian Medicinal Plants in two volumes for CSIR.

**D.S. Bhakuni (partly with R.S. Kapil)** had a prodigious output in natural products chemistry apart from synthetic work. His group had many successes in isolation and structure determination of protoberberine, proaporphine, aporphine and bisbenzylisoquinoline alkaloids - isococculidine 31 from *Cocculus laurifolius* DC and cocsulinine 32 from *Cocculus pendulous* Forsk are cited as two examples.¹

![Isococculidine](image2.png)

Carrying forward the expertise of studying biosynthesis using C14 labelled precursors which Bhakuni and Kapil had acquired in the laboratories...
of D.H.R. Barton and A. Battersby respectively, the former duo have done trail blazing work in India in tracing biosynthetic pathways of several alkaloids. Special mention must be made of Bhakuni’s work on the determination of the absolute configuration of tiliacorine. Bhakuni was one of the earliest, if not the first to investigate marine plants and animals from East and West coast of Andaman and Nicobar.

5.7 University College of Science, Calcutta has had a continuous tradition of carrying out natural products research of a high standard.

The work of P.K. Bose and Asima Chatterjee has been already covered.

S.K. Talapatra, mentored by Asima Chatterjee, had an active group working on various constituents of plants such oxygen heterocycles eg murralongin from Murraya elongata.

Julie and Avijit Banerji, daughter and son-in-law respectively of Asima Chatterjee have nurtured the tradition of natural products research in the University College and made contributions, e.g. serdaferin, a new sesquiterpenid coumarin from Ferula asafoetida and a carbazole alkaloid from Murraya koenigi, and flavanoids from Pongamia glabra.

5.8 Calcutta School for Tropical Institute and Indian Institute of Experimental Medicine

R.N. Chopra’s contributions have been mentioned earlier. R.N. Chakravarti during 1948 to 1978 did pioneering work on isolation of diosgenin from Diascoria deltoidea and solasodine from Solanum khasianum, both important for synthesis of steroid hormones.

5.9 Bose Institute of Calcutta

We had noted earlier that Dr. P.K. Bose was in this institute in the 1940s (Dr. S.C. Battacharyya joined this later in 1978.) Some interesting results obtained by two other natural products chemists there in the period 1960-1980 may be mentioned.

Dr. D.P. Chakraborty carried out a thorough investigation of the novel carbazole alkaloids of Murraya koenigii, the curry plant – girinimbin, mahanimbin, murrayarin and others. He has also written a review – Carbazole Alkaloids. We shall see later that N.S. Narasimhan and B.S. Joshi in other parts of the country were simultaneously working on this popular plant.

P. Chakraborti was investigating triterpenoids during that period – isolation and structure determination of the sapogenin, mollugogenol A from Molluga hirta Roxb.
5.10 Indian Institute of Chemical Biology, Calcutta

S.C. Pakrashi, coming from the school of Asima Chatterjee, has spent over three decades in the chemistry of natural products and made very important contributions to the chemistry of indole and oxindole alkaloids from Vinca, simple quinazolidine alkaloids from *Glycosmis arborrea* and novel benzopyrido quinolizidines from *Alangium lamarckii* e.g. alamaridine \(^{36}\) and synthesis. The last plant also yielded bharatamine \(^{37}\), a unique protoberberine alkaloid biogenetically derived from a mono terpenoid precursor. \(^{22}\) His researches also uncovered new sesquiterpenes, triterpenoids and spirostane saponins and sapogenins, and a unique steroidal alkaloid, solanocrisine. Pakrashi’s interests extended to marine natural products also e.g. isolation of epoxylipids from marine invertebrates and sulphonoglycolipid from the green alga.

36. Alamaridine

37. Bharatamine

5.11 Kalyani University

P. Sengupta came to Kalyani University after already carrying out work of high standard at East India Pharmaceuticals (remarkable that such work could be done there) and continued to investigate plants. During the period 1960 -1980 he isolated terpenes and other constituents eg from the neem tree, *Azadirachta indica*, a norditerpenoid, nimbiol and also the bitter principles, nimbin for which a partial structure was given. The full structure was provided by C.R. Narayanan and N.S. Narasimhan. Sengupta settled the structure of psoralidin, a benzocoumarin from *Psoralea corylifolia* Linn as \(^{38}\). \(^{23}\)

38. Psoralidin

5.12 Andhra University, Waltair

The work of T.R. Sheshadri and S. Rangaswami has been already covered. L. Ramachandra Rao, a student of T.R. Seshadri, continued the tradition of study of natural products with unabated vigour. Investigation of *Tiliacora racemosa* yielded tiliacorine \(^8\) whose partial structure was derived. The structure of arjunic acid from *Terminalia arjuna* was established as \(^{39}\) with a triterpene scaffold. \(^1\) His student, S.R. Anjaneyulu maintained the tempo of natural product research.

39. Arjunic acid
5.13 Indian Institute of Chemical Technology (formerly Regional Research Laboratory), Hyderabad

With full-fledged facilities the institute has been having a continuous engagement in natural products research which is currently having a team under S. Chandrasekhar in isolation and structure determination. Earlier J. Madusudhana Rao had been very active. Y. Venkateswarlu with prior experience with marine natural products, under funding from Ministry of Earth Sciences, has isolated from the soft coral, *Sinularia dissection*, Rameswaralide, a novel diterpene with anti-inflammatory activity, whose structure has been assigned as 40 in a collaborative project. He had also isolated xestospongin from a marine source. G. Srinanarayana was an active researcher at Osmania University, Hyderabad.

5.14 Presidency College, Madras

B.R. Pai collaborated with T.R. Govindachari in plant product research from 1950 until the later moved over to Ciba Research Centre in 1963. Pai continued the tradition maintaining the Ciba collaboration until he retired from Presidency College, working on coumarins and protoberberines. He continued the work at Amruthanjan Research Centre.

S.N. Chakravarti (Annmalai University), Sankara Subramanian (Jipmer, Pondicherry) and S. Neelakantan (Madurai Kamaraj University) were involved in investigation of Indian medicinal plants. The last two had been mentored by T.R. Sheshadri.

5.15 Indian Institute of Science, Bangalore

The early contributions of J.L. Simonsen (around 1920) and P.C. Guha (1935 – 1955) have been noted. After possibly a long break, the thread was picked up around 1970 by G.S.R. Subba Rao whose research concerns embraced structure elucidation of natural products isolated from indigenous medicinal plants apart from a few others such as total synthesis and reduction by dissolving metals in liquid ammonia. His work on plants resulted in isolation of antitumor diterpenoids like calyenone, sesquiterpenes, triterpenes, limonoids, lignans like phyllanthin and hypophyllanthin and complex xanthones. Moreollin 41 from *Garcinia morella* is an example of the last class.

5.16 University College of Agricultural Sciences, GKVVK campus is home to a few scientists involved in the study of natural products.

R. Uma Shaankar has avid interest in plant evolutionary biology, conservation genetics and bioprospecting. His group has discovered rich sources of the anticancer alkaloid, camptothecin in western ghat plants. Although this alkaloid did not make it to the market, semisynthetic drugs derived from it like topotecan and irinotecan are clinically used drugs. Likewise plants have been identified as rich sources of shikimic acid which is the important starting material for the valuable antiinfluenza drug Tamiflu. The group has also isolated two new catechols from *Semicorpus anacardium* with potent acetyl cholinesterase inhibitory activity.
Another scientist, K. Chandrashekara is interested in peptides with activity from wasp venom; peptides with 13 and 16 amino acids have been isolated and the structures identified in collaboration with P. Balaram.27

K.N. Ganeshaiah is doing remarkable work in establishing a bio-resource database. He has established an Indian bio-resource network (IBIN) and created Jeevasampadha (species data).

5.17 ESKAYEF Research Centre, Bangalore during 1971-1987 carried out antibiotic research by fermenting various soil samples and isolated some new antibiotics.

5.18 National Chemical Laboratory, Pune was an acclaimed centre for research in natural products chemistry. The contributions from K. Venkataraman, S.C. Bhattacharyya and Sukh Dev have been noted. C.R. Narayanan was another well known scientist for his works on terpenoids. One of his major achievements was solving the structure of nimbin together with N.S. Narasimhan as 42, a complex modified triterpene.1 This bitter principle had been isolated from neem by Siddiqui. B.A. Nagasampagi had a group which did extensive work on plant products.

5.19 Pune University Department of Chemistry had a flourishing school of natural products chemistry from 1960 onwards. N.S. Narasimhan, from the group of T.R. Govindachari had joined the department and led a group of students in isolation, structure elucidation and synthesis of natural products. Extending his earlier work on the alkaloids of Carica papaya, he deduced the structure of pseudocarpaine, and on neem, the structure of nimbin 42 (together with C.R. Narayanan). One of his notable contributions was the isolation of eight alkaloids from Murraya koenigii, the curry plant and recognition of the carbazole scaffold in them. Mahanimbin 43 is cited as an example.1 He also made rich contributions to natural product synthesis through hetero atom directed lithiation reactions.

5.20 Hindustan Antibiotics Limited, Pimpri, set up in the public sector for the manufacture of life saving penicillin antibiotics, also carried out basic fermentation studies. A polyene antifungal antibiotic, named hamycin, isolated in their laboratory, subsequently turned out to be a mixture of known molecules.

S.K. Paknikar, mentored earlier by S.C. Bhattacharyya, set up a school of natural products chemistry in the University of Goa. The National Institute of Oceanography of CSIR has been carrying out research in marine products in collaboration with other institutions.

5.21 Ciba Research Centre (later Ciba-Geigy Research Centre, 1963 – 1989): After its inception, under the leadership of T.R. Govindachari it became a renowned seat for natural products chemistry research. Some of the contributions have been recorded under T.R. Govindachari

With a mandate to develop drugs from Indian plants the natural products group consisting of B.S. Joshi, N. Viswanathan and P.C. Parthasarathy carried out a systematic extraction of plants and had the activities of the extracts
monitored by the biology group. Structural studies were an integral part of this work and resulted in identifying many novel molecules. Identification of *Nothapodytes nimmoniana* as a rich source of camptothecin was an important outcome. Semisynthetic derivatives are useful anticancer drugs.

**B.S. Joshi**'s interests encompassed alkaloids, sesqui, di and tri terpenoids, flavanoids, coumarins, lignans and quinones. Some representative examples are heayneanine, piper alkaloids (review in *Heterocycles*), eg piperstachine, cyclostachine A 44, cyclostachine B, terpenes, furanogermacrolides like zeyleanine, veprisone, 3-epicyclopertin (with marked insect antifeedant properties), ailanthol 45 and oxygen heterocycles, talbota flavone 46, surangin B 47.

### 5.22 Bhabha Atomic Research Centre, Bombay

The bioorganic chemistry division, initially headed by M.S. Chadha hosted a flourishing school of natural products research in several dimensions - microbial transformations example of flavonoids, biosynthesis of natural products in both in vitro and in vivo systems and most importantly, tissue culture studies on alkaloid barring plants like *Tylophora asthmatica* and *Atropa belladona*. The tempo was maintained by N.B. Mulchandani, A. Bannerji, V.R. Mamdhapur and S. Chattopadhyay.

### 5.23 Hoechst Research Centre, Bombay (1972 – 1998)

The centre had thriving and extensive natural product research on plant products as well as antibiotics from fermentation. Working on the lead of rohitukine, a chroman alkaloid an analogue, flavopiridol was developed into an orphan drug for a type of cancer in US. The isolation of forskolin, an active principle of *Coleus forskohlii* (also found at CDRI and called coleonol – Merck Index name, Colforsin 29) together with...
the enormous biological and chemical work at Hoechst to exploit its positive inotropic activity can be considered as a major piece of research.29

The development of water soluble cyclodextrin complex by Sami Laboratories has been noted earlier.

5.24 Piramal Life Sciences, Mumbai

The company with a full fledged research centre for new drugs, partly after acquiring Hoechst Research Centre, has been very active in natural products research. Collaborating with National Institute of Oceanography, they isolated from a marine organism, *Kocuria palustris*, a macrocyclic thiazole peptide antibiotic, PM 181104 now identified as Kocurin 48 30. This molecule has potent activity against gram positive bacteria including MRSA and VRE resistant ones.

5.25 Maltichem Research Centre, Baroda – covered already under Sukh Dev

Piramal is also studying a microorganism belonging to the Streptomyces species from *Schirmahar Oasis* region in Antarctica and has isolated two thiazolyl peptide antibiotics having potent antibacterial and antimycobacterial activities.31

5.26 Ahmedabad textile Industry Research Association (ATIRA)

H.C. Srivastava, a renowned carbohydrate chemist, worked at ATIRA for nearly three decades. He always felt that India had a great potential in the area of carbohydrate chemistry and its applications. He published about 150 papers in polysaccharide chemistry and trained 29 Ph.Ds. He is a co-author of the book, Structural Polysaccharide Chemistry.

While there are some centres in India where carbohydrate chemistry as part of naturally occurring glycosides is studied, there are others where natural polysaccharides from terrestrial and marine resources are investigated, especially their applications. A partial list is given below:


6. Conclusion

The foregoing report reveals that chemistry of natural products, mostly from plants and to a much lesser extent from marine resources has been a continuous activity in India for just over a century in terms of isolation and structure determination. Indian chemists have uncovered many unique, novel structures which were the first of their kind. This has been well recognized in international scientific fora. Much of the earlier work was carried out under far from ideal conditions and is all the more remarkable. The activity peaked between 1960 and 1980 and seems to be falling off despite far more facilities being available now, action occurring mostly in some national laboratories and a few elite institutions.
One of the reasons is undoubtedly that such work has gone out of fashion but there seems to be some revival in the international scene. Indian chemists must take advantage of the facilities and also the availability of a vast store house of flora in India, still unexplored. Since isolation and structure determination are no more the severe challenges they were in the past, interest in such products must be evoked for basic exploration of unanticipated diversity and potential usefulness in areas like diseases, human and animal and crop protection. These exercises must be broadened and strengthened in their scope by pathway engineering/chemical biology. India’s marine sources still wait to be explored and exploited fully. Fermentation as a source of antibiotics is an understudied area in India which has good potentials. The country now offers adequate facilities and attractive incentives. What are needed are skilled, motivated and dedicated researchers who can inspire newer generations of younger minds. This calls for a national policy, enunciated clearly and expressed loudly, for a new thrust in the area of natural products research.

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