# Professor Sukh Dev

## A Tribute

Sukh Dev was born to Hari Chand Lala and Maya Vanti at Chakwal (undivided India, now in Pakistan) in June 1923. He started his career in chemistry in 1944 and graduated at D.A.V. College, Lahore (M.Sc. 1945), and later carried out research at Indian Institute of Science, Bangalore (Ph.D., 1950 and D.Sc. 1960). Professor Sukh Dev has been engaged in organic chemistry research for more than half-a-century, and has moved through the laboratories of Indian Institute of Science, Bangalore (1945-1959), to the National Chemical Laboratory, Pune (1960-1974), to the Malti-Chem Research Centre, Nandesari (1974-1988), to Indian Institute of Technology, New Delhi (1989-1993) and at present in Delhi University as a visiting professor in Dr. B. R. Ambedkar centre for biomedical research. As he moved from one institution to another, the thrust of his research effort underwent shifts in consonance with spirit of the institution, ranging from curiosity-oriented investigations to market driven industry/technology oriented research. Professor Sukh Dev's research interest covered a broad range from natural products chemistry, non-benzenoid hydrocarbons, organic reactions, reagents and techniques, drug development from Ayurvedic leads, to technology development. All this activity has led to significant contributions (>375 publications including 50 patents, 92 Ph.D. dissertations), which have been well recognized both nationally and internationally (received a large number of awards and became a fellow of several science academies). He served as a member of the Editorial Boards of Tetrahedron and Tetrahedron Letters (1976-1995), Tetrahedron Asymmetry (1990-1995) and Dictionary of Organic Compounds (5th edition). The following account summarises Professor Sukh Dev's major contributions.

### Natural Products Chemistry

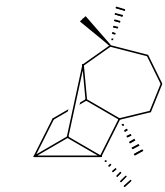
This has been the main area of activity of Sukh Dev, to which he had got exposed while working for his Master's and Doctorate's dissertations at Lahore (1944-45) and Bangalore (1945-48), respectively. At the Indian Institute of Science, Bangalore, which had a long tradition of research in essential oils and terpenes, he could see an impressive collection of oleoresins, resins, essential oils and terpenes of the country, and this kindled in him a lasting interest in this area of natural products chemistry. Though, work on certain woods, oleoresins and essential oils was initiated at the Indian Institute of Science, a much bigger and sustained effort could be organized only at the National Chemical Laboratory, Pune, where he had moved by the end of 1959.

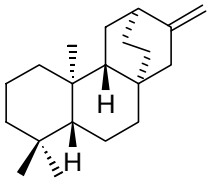
Classically, work in natural products had invariably been a difficult and time-consuming undertaking, and many complex and novel molecules had resisted structure elucidation till 1950.

However, with the advent of modern spectroscopic methods, the situation started changing around 1950, and in the next one-and-a-half to two decades it had undergone complete metamorphosis. Structure determination then became vastly simplified. With these developments, emphasis in the natural products chemistry shifted to biologically active molecules or compounds with novel structural features. Prof. Sukh Dev's efforts in these directions led to the discovery of several new structural types in terpenoids, as well as characterization of active principles of some Ayurvedic drugs.

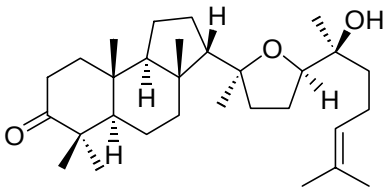
Prof. Sukh Dev's group is responsible for the isolation, chemical studies and determination of absolute stereostructures of scores of new complex molecules such as: zerumbone, longicyclene, himachalenes and related compounds, mayurone, mustakone, rotundone, cuparenones, lac constituents, hardwickiic acid, mukulol, devadarol and related compounds, cheilanthatriol, malabaricol, bakuchiol, kodocytochalasins, etc. Many of these compounds represent new fundamental types in nature and have been termed "classics" (*C & EN*, Sept 1979, p 63).



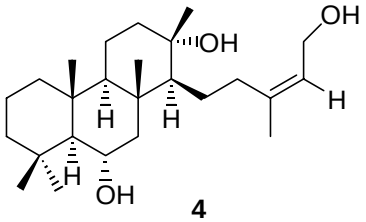
**1**
Longicyclene



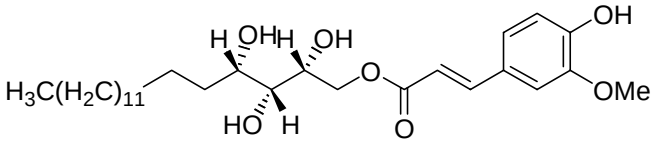
**2**
Atisirene



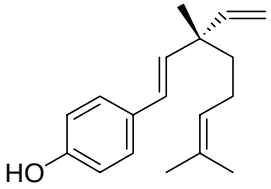
**3**
Malabaricol



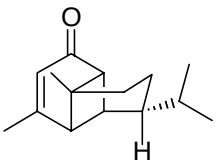
**4**
Cheilanthatriol



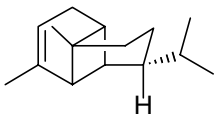
**6**
$C_{18}$-Guggultetrol ferulate



**5**
Bakuchiol



**7**
Mustakone



**8**
(+)-Copaene

Thus, longicyclene (**1**) was the first tetracyclic sesquiterpene; atisirene (**2**) was the first example of a nitrogen-free tetracyclic diterpenoids of atisine type; malabaricol (**3**) was the first tricarboxylic triterpenoid arising from a biogenetically very significant cyclization; cheilanthatriol (**4**) was the first sesterterpene with the "triterpene-type" ring-closure; bakuchiol (**5**) was the first meroterpene derived from $C_8 + C_{10}$ pathway; and, guggultetrols (e.g. **6**) represent a new class of lipids. Structure determination of mustakone (**7**) led to the revision of long-held structure of the classical

sesquiterpene copaene (**8**). Biogenetic considerations played a key role in these structure determinations which were carried out, when the modern 2- and 3-D NMR techniques had not yet been developed.

Based on the work of Sukh Dev's school and a careful evaluation of the published literature, he has proposed two useful rules: (1) *The Absolute Stereochemistry Biogenetic Rule:* The absolute stereochemistry of various constituents of a given class of natural products in a given tissue must have the same (or derivable there from) absolute stereochemistry at a common reference point (unless each compound is formed by an independent one-step process, which is considered unlikely). (2) Exotic biological materials tend to produce exotic secondary metabolites.

A classical aspect of natural products chemistry concerns their chemical reactivity. Nature often produces molecules that are structurally strained or have such built-in stereoelectronic features that under slightest provocation (chemical, photo or thermal) undergo reorganization. This has, in the past, generated interesting and unexpected results, often of fundamental importance. Sukh Dev's group has eminently investigated reactions of many natural products, and these efforts have unfolded novel transformations and rearrangements (e.g. see Fig. 1), both of academic and commercial value. Detailed chemical studies on longifolene and isolongifolene led to this concept of 'Steric Diversion' and a new fragmentation reaction. A number of perfumery materials based in isolongifolene are in the market world-wide.

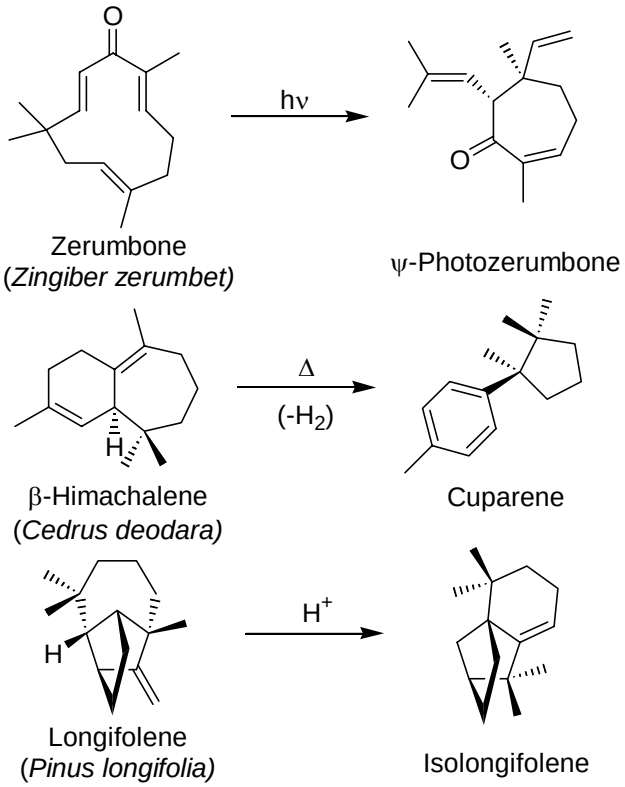
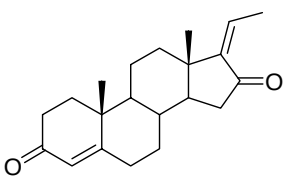



**Figure 1.** Rearrangements of some terpenoids.

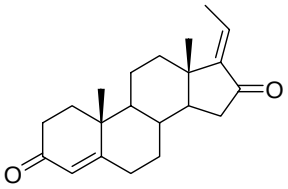
## Drug development from Ayurvedic leads

Sukh Dev was the first to emphasize that while investigating ayurvedic crude drugs or other medicinal plants, one must specifically look for the biological activity for which the drug is renowned in ayurveda or folklore. His group's work in this field has amply demonstrated the value of this approach. Thus, from *Guggulu*, the gum-resin of the tree *Commiphora mukul*, well-known in ayurveda for the treatment of lipid disorders, his group was able to isolate two steroidal ketones (**9** and **10**) with pronounced hypocholesterolemic and hypolipaemic activity. A modern hypocholesterolemic drug based on these results is in the market now. Shatavarin-I (**11**) was demonstrated as the anti-oxytocin principle of Shatavari (roots of *Asparagus racemosus*), a drug recommended in ayurveda for the treatment of threatened abortion. In conformity with the use of *Cedrus deodara* wood oil for the treatment of various skin diseases of cattle, Sukh Dev's group was able to demonstrate that himachalenes, occurring in the essential oils have a useful broad-spectrum activity against a variety of ectoparasites (fleas, ticks, mites, lice). A veterinary drug based on these findings has been marketed.

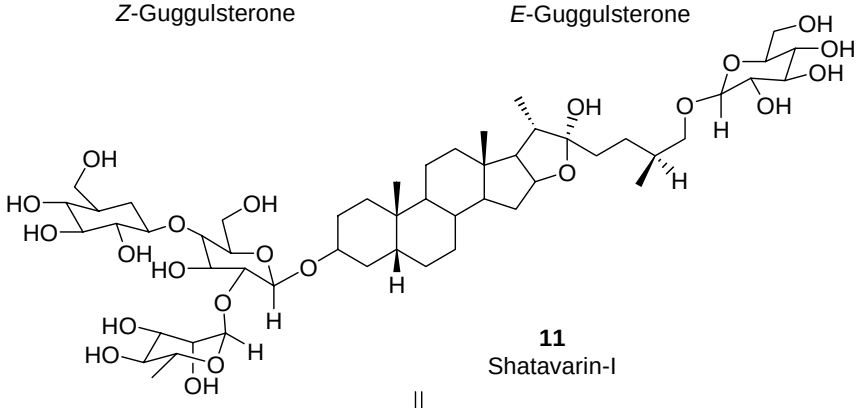
Kodo millet (*Paspalum scroliculatum*) is a minor grain crop of India, but has occasionally been reported to cause poisoning in man and animals when used as food. His group demonstrated that the toxins are kodocytochalasins (**12** and **13**), metabolites of fungus *Phomopsin paspalli*, a pathogen of kodo millet.



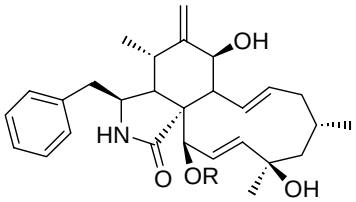
**9**
*Z*-Guggulsterone



**10**
*E*-Guggulsterone



**11**
Shatavarin-I



**12** R = Ac; Kodocytochalasin-1
**13** R = H; Kodocytochalasin-2

In late eighties and early nineties, Sukh Dev's group has been engaged in evaluating Ayurvedic crude drugs using receptor-binding technique; Several useful leads have been uncovered. For example, from the fruits of *Terminalia bellirica* (Sanskrit : *Bibheetak*) highly prized in ayurveda for treatment of gastrointestinal ailments, two compounds with remarkable affinity for cholecystokinin (CKK) receptor have been isolated. CCK hormones play a vital role in gut function, regulation of feeding habits and digestive process.

**Azulenes and other non-benzenoid aromatic systems**

In the fifties and sixties there was considerable interest in azulenes, tropones and, in general, in non-benzenoid aromatic systems. During this period, Sukh Dev devised several methods for their synthesis and characterization, and proposed novel systems with potential aromatic character. Special mention may be made of ring-expansion of indanes with diazomethane under photoirradiation to furnish azulenes, synthesis of *S*-guaiazulene, *Se*-guaiazulene, trimethyleneazulenes, 11*H*-indeno[2,1-a]azulene, and tropones and tropylium salts.

**Reactions, reagents and techniques**

Sukh Dev has also made outstanding contributions in the area of organic reactions and reagents. He and his students did extensive work on the use of polyphosphoric acid for intramolecular acylation of γ- and δ-lactones to furnish cyclopentenones, and has become classic and the reaction is used commercially for the manufacture of dihydrojasmone, a useful aroma chemical.

His group was the first to investigate (1965) in a systematic manner organic reactions in a solid matrix, a concept and technique now widely practiced.

Amongst other contributions falling in this category, mention may be made of: composite amine catalysis for Knoevenagel-type condensations, chromic acid for oxidative work-up of ozonides, thiourea for reductive cleavage of olefin ozonolysis products, titanium tetrachloride for thioacetalization and, improved Lindlar catalyst for semihydrogenation of acetylenes.

His group was the first to introduce (1962) the use of silver nitrate-silica gel for thin-layer chromatography of olefins, a technique now used world-wide, and which had a profound effect on investigations in the area of natural products chemistry, especially terpenoids and steroids.

**Technology development**

Sukh Dev's interaction with industry started at the National Chemical Laboratory, Pune, but his stint at Malti-Chem Research Centre, Nandesari (1973-88) was mostly devoted to technology development based on original research. Thus, a molybdenum oxide promoted Raney nickel catalyst was developed for facile hydrogenation of glucose to sorbitol and several thousand tonnes of sorbitol is now made world-wide by this process. Likewise, a copper-nickel-manganese catalyst for the dehydrogenation of cyclohexanones to phenols was developed, and thymol has been produced from the readily available menthones by this method.

The highlight of Sukh Dev's activity in this area is the way his group has demonstrated the value of restructuring abundantly available natural products into chiral molecules of economic value. Thus, the optically pure (+)-3-carene, the chief hydrocarbon of Indian turpentine (ex *Pinus roxburghii* Srg. syn. *P. longifolia*) has been restructured to produce an array of low volume, high-

value compounds of commercial interest, in the correct optically active form, by methods which are commercially viable. Processes, thus developed, include routes to (-)-menthol, (+)-carvone, (+)-mentha-2,8-dienol (a valuable raw material for the synthesis of Δ'-tetrahydrocannabinol, an antinauseant for cancer patients undergoing chemotherapy), and pyrethroid intermediates (+)-chrysanthemic acid, (-)-caronaldehyde acid hemiacetal and (+)-pyrethric acid. To demonstrate the possible value of the resin from *Commiphora mukul* as a new steroidal raw material, his group transformed guggulsterones into the valuable glucocorticoid, dexamethasone.

Bakuchiol (**5**), which has a weak juvenile hormone activity, has been converted into a potent juvenoid with good promise for use in sericulture.

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