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Turmeric – botany, chemistry, mode of working and metabolism

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Abstract
India is the global leader in turmeric production and generates considerable foreign exchange through export of its rhizome and many value-added products. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin, all yellow-coloured crystalline solids with a characteristic aroma and collectively referred to as curcuminoids, are the constituents of economic and biological significance present in the rhizome of the plant, a member of Zingiberaceae family. Of the three constituents, curcumin is the most abundant and functionally active. Curcuminoids are unsaturated polyphenolic substances with keto and other functional groups, and do have therapeutic, culinary and cosmetic applications. The therapeutic use is largely due to their antioxidant, anti-inflammatory and wound healing activity. However, a major deterrent in making the best use of the therapeutic potential of curcuminoids is their poor bioavailability at the site of action. Several approaches such as co-application with adjuvants and augmenting its sustained release at the target site are in practice to overcome the said defect. Curcuminoids are rapidly metabolised in human biological systems, principally by biochemical reductions requiring NADPH and conjugation reactions, primarily with glucuronides and sulphates, and are excreted out of the body, mostly through faeces.

Keywords: Rhizome, curcumin, tautomerism, conjugation, antioxidant, anti-inflammatory, Reactive Oxygen Species (ROS), Super Oxide Dismutase (SOD), COX-2, bioavailability

Introduction

One among the plants that occupies a high place in Indian culture, sentiments and ethos is turmeric (Haldi or Indian saffron). The economic value and cultural significance of the plant is almost entirely due to the bright yellow pigments present in the plant's rhizome, a modified stem that grows underneath the soil, as found also in few other familiar plants *viz.* ginger, lotus and bamboo. The name 'turmeric' has its origin in the Latin word '*terra merita*' meaning 'meritorious earth', presumably referring to the plant's valued use, especially of the golden hued paste prepared from the rhizome. Turmeric finds a prominent and enduring presence and uses in many Indian ceremonies and festivities, such as religious observances and the traditional pre-wedding ritual in many regions, where the bride and the groom are smeared with a turmeric paste. For a common man, the plant is much known for its use in the kitchen for adding a characteristic colour and aroma to the curries and other food dishes and delicacies. Also, the plant is well known also for improving the complexion of the skin. Turmeric is a celebrated plant for its diverse medicinal properties in dealing with health disorders ranging from diabetes and hypertension to mental stress, all associated with today's high paced modern life and obsession with junk food. Ayurveda and Atharvaveda document the medicinal use of turmeric as an ancient home remedy dating back to more than five thousand years. Justifiably, the plant has been receiving increasing attention from the researchers and public for its multi-faceted properties. This is more so because of a steady increase in the use of medicinal plants and herbal products in health care and in boosting the body's immune system to ward off pathogens and parasites, a concept that got firmly embossed in public psyche after the outbreak of Covid-19 (SARS-CoV-2) pandemic in early 2020. This awareness and shift from modern medicines and chemicals to plant-based products is mainly to keep off the accompanying ill effects of the former. And turmeric is a front ranking plant in the current context. Use of turmeric as such and a range of value-added products prepared from the rhizome has substantially increased in recent years. It is thus an opportune time to know more about this wonder ancient Indian plant, its botany, cultivation and contribution to Indian economy, health benefits, chemistry, pharmaceutically active constituents and their metabolism, and focus areas of future research work.

Turmeric in India

Available records suggest turmeric to have its origin in India. Marco Polo, the great 13th century Italian explorer, noticed the use of the plant in Southern India for dying clothes and in religious ceremonies as offerings to God while praying for peace, prosperity, purity and endurance. Marco Polo in his jottings referred the plant as Indian saffron. The plant later spread to other parts of the globe and is now extensively cultivated in India, and southeast Asian region, and in some South American and Caribbean countries *e.g.* Sri Lanka, Taiwan, Indonesia, China, Myanmar, Jamaica, Peru and Haiti. Turmeric finds a prominent place in Indian economy. India accounting for nearly 80% of the total global produce is the largest producer and consumer of turmeric. India's total acreage under turmeric is about 300,000 ha, while the total rhizome production hovers around 1.2 million tonnes. Among the states, Telangana and Andhra Pradesh are the front rankers and together they alone contribute to nearly half of the turmeric acreage and production. Other notable states, but well behind them, are Maharashtra, Karnataka, Tamil Nadu and West Bengal. Duggirala (A.P.), Nizamabad (TG), Sangli (MH), and Dharmapuri and Erode (both in TN) are some of the major turmeric growing and trading centres of India.

Uses

Few plants do have as diverse uses as turmeric *viz*. culinary, cosmetic, medicinal, food preservation, dyeing, and aesthetics. Various oriental systems of practicing medicine *viz*. Ayurveda, Unani and Siddha, and ancient Chinese medicine amply quote the medicinal uses of turmeric. Applying a paste of the plant's rhizome is well documented in traditional, contemporary and alternative medicine. In India and its neighbouring countries, turmeric has been used as a home remedy for centuries for wide-ranging ailments. Even today, a hot turmeric paste is in use in Indian households as a quick relief and remedy for sprains, insects' bites, itches, minor cuts, burns and bruises. For use in medicine, both preventive and curative, there are many 'ready to use' turmeric containing pills, capsules, ointments and creams available in retail outlets. Also, there are several turmeric based branded cosmetic products, especially for use in skin toning. On the culinary side, the rhizome because of its intense yellow colour and spicy aroma has been a natural choice for seasoning curries and a range of kitchen savouries in India and neighbouring countries. The plant's finely ground dry rhizome or commercial curcumin (the yellow pigment of the plant) extracted from the rhizome finds use also in many processed foods that include among others rice-based delicacies, popcorn, sauces, pickles, yellow cakes, mayonnaise, yoghurt, baked products, milk, dairy products, orange juice, ice cream and canned beverages. In food industry, curcumin or turmeric finds use for adding colour to many processed foods *viz*. dairy products, fats, oils, ice creams, fruits and vegetable products, bakery and confectionery, meat and meat products, fish and egg preparations, soups, sauces, beverages and blanched products. Turmeric finds use also in non-alcoholic beverages, poultice, and as a dye in textile industry. Turmeric has justifiably emerged as a cheaper and nearly equally effective alternative to saffron across the globe.

Production and Export

Global production of turmeric is around 1.5 million tonnes per annum of which India alone accounts for 75 to 80%. Other major producers are Vietnam, China, Indonesia, Myanmar, Nigeria and Bangladesh. Turmeric is in high demand in global import export market. Among all countries across the globe, India is the largest exporter of turmeric with its share not less than 60%. Indian turmeric because of its high curcumin content is in high demand in its global trade. The crop in India thus generates a substantial amount of foreign exchange reserve. However, the demand is very high and there is much more to achieve in its export. India's domestic demand of turmeric is very high and as much as 85% of the total produce goes towards meeting the country's own requirement. Only the rest of about 15% is exported in the form of unprocessed turmeric rhizome (9%), turmeric powder (5%) and quite a few high value-added products (2%). There are more than a hundred and fifty destination countries among which USA, Iran, UAE, Malayasia, UK, Germany and Japan are the lead ones. Further, global trade demand of turmeric has increased substantially since the last couple of decades, primarily because turmeric and its products have been receiving increasing public acceptance in the western world due to its health benefits with no side effects. To take advantage of this demand, the Government of India has chalked out a plan for an ambitious target of earning foreign exchange to the tune of 1 billion USD through its export by the year 2030. Some of the important steps in reaching this high target are encouraging turmeric growers for more acreage, protecting their interests, providing them a technical know-how in its cultivation that includes varietal selection, pests and disease control measures, adopting improved package of cultivation practices and water economy, harvest and post-harvest care, guaranteeing them a financial security, and lastly regulating the market arrivals of the produce, giving due consideration to glut and storage facility. Other factors, no less important than those mentioned, are developing new and novel turmeric based value-added products and exploring new and more lucrative export markets. Towards realising the mandates as stated and additionally harnessing the untapped potential of turmeric, the Ministry of Commerce and Industry of the Government of India established the National Turmeric Board with its HQ at Nizamabad in Telangana in June, 2025.

Botany and Cultivation

Turmeric (*Curcuma longa* L., synonym *Curcuma domestica* Valeton) is a plant of Zingiberaceae family of which few other important members are ginger, cardamom and galangal. Kasthuri manjal (*C. aromatica*), a wild variant of the species, especially used for cosmetic and medicinal property, is in limited cultivation in India and China. Less important species are *C. xanthorrhiza* (Japanese Ginger), *C. heyneana* (Japanese Giring Ginger) and *C. zedoaria* (White turmeric). These largely similar looking species contain characteristically different amounts of curcuminoids, the active ingredients of the species, so much so that a particular species can be identified by the said content. Turmeric is a tropical or subtropical crop plant and is cultivated as a rainfed or an irrigated crop at an of altitude to 1200 m above MSL. In India, turmeric sowing starts in June-July coinciding with the onset of the Southwest monsoon. Among the cultivars, Lakadong, Duggirala, Sangli, Vasmat, Mydukur, Armoor, Tekkurpet, Amalapuram, Salem and Erode are much preferred by the growers in their respective areas. Some of them have acquired GI tags too, helping in protecting and conserving their genetic stock. Among the long list of the improved high yielding varieties, growers' choice is for Suvarna, Suguna, Sona, Sobha, Sugandha, Suroma, Surangi, Sudarsana, Varna, Rashmi, Phule Swarupa, Roma and Uttar Rangini. The plant is a 60 to 90 cm high perennial flowering herb with 38 to 45 cm wide and 76 to 125 cm oblong 7 to 12 leaves with a unique aroma. The leaf sheath forms the pseudo stem. The hermaphroditic flowers, zygomorphic and trimerous, born in axil of the bract opening one at a time, are lilac white. Flowers are, however, sterile due to imperfect or malformed stamens and ovaries, making propagation of the plant by vegetative means, a mandatory reproductive process in which the bud or an eye of the rhizome acts much like a seed. Rhizome, the economic part of the plant, gets ready for harvest in 7 to 9 months (200 to 260 days), making turmeric a long duration crop. For generating some additional revenue during the long growing period, usually a short duration crop with demand in the local market is raised along with turmeric as an inter crop or a mixed or a border crop. Some of the well-suited crops for the purpose are chilli, onion, red gram, colocacia, sun hemp, brinjal and okra. Cereal or millet crops such as maize and ragi also suit well; at times, green

manuring and fodder crops like guar, cow pea and dhaincha are also preferred along with by the growers for enriching the soil or feeding the livestock. Rhizome yield under good agronomic management practices with no waterlogging and soil alkalinity, the two conditions to which the crop is extremely sensitive, is about 30 tons/ha. For use and trade, the harvested rhizomes are to be processed requiring another 10 to 15 days time.

Post Harvest Processing and Extraction of Curcumin

The harvested rhizomes (2 to 8 cm long and 1 to 2 cm wide fingers, bulbs and splits) are allowed to stand undisturbed for 3 to 4 days for ageing, washed with water, boiled (45 to 60 min for the fingers and 90 min for the mother rhizomes), and then subjected to dehydration. The latter by conventional sun drying turns out to be a prolonged cumbersome process apart from falling short in quality retention. This makes freeze drying to be a much better choice in turmeric processing in commercial scale. The washed, boiled and dried materials are then polished by mechanical rubbing for an appealing appearance and graded as fingers (daughter rhizomes, up to 7.5 cm long), bulbs (mother rhizomes, wider and shorter than fingers) and splits before being sent to the marketing centres. Upon such processing, fresh raw turmeric rhizome reduces to about only 20 to 25% of its original mass. To meet the market requirement, the processed rhizome material is finely ground to secure turmeric powder for culinary and other uses. Further, for making turmeric based high value-added products for use in cosmetics, dietary supplements and herbal pharmaceuticals, curcumin, the principal yellow coloured substance present in the rhizome, needs to be extracted. For the extraction, the dried rhizomes are cut into bits of convenient sizes and macerated. Solvent extraction coupled with column chromatography is widely followed for the extraction process. Routinely used polar and non-polar organic solvents used for the extraction of curcumin from turmeric rhizome are *n*-hexane, ethyl acetate, acetone, *iso*propanol, butanol and methanol. *C*hlorinated solvents *e.g.* methylene chloride are more efficient in extraction but are not preferred because of their toxicity and non-acceptability in food industry. For dietary and pharmaceutical use, food grade solvents like triacylglycerols or deep eutectic solvents specifically designed keeping in view the substance to be extracted and the major unwanted co-extractives to be eliminated are fast emerging as safer and better choice extractants on account of their no toxicity, low vapour pressure, biocompatibility, lesser environmental hazard and most importantly, their greater efficiency in the extraction process. Other extraction processes such as Soxhlet extraction, ultrasonic extraction, fractional crystallization, dipping and zone-refining, pulse ultrasonic process and microwave-assisted extraction methods are in limited use. Increasing the temperature to 60 to 80 °C during extraction hastens up the extraction process. A relatively new safe, efficient and economically viable extraction process uses supercritical carbon dioxide, operated at 45 ^{0}C and 25 to 30 MPa pressure. Enzyme-assisted extraction, using α-amylase and glucoamylase, though expensive right now, is a process with future promise. The extracted material further purified by recrystallization from a suitable solvent produces a crude product. The latter is a mixture referred to as curcuminoids, also known as Indian saffron, yellow ginger, natural yellow and root yellow. The mixture contains small amounts of coextracted oils and resins also. Curcuminoids account for 3 to 5% of the dry biomass of the rhizome of the plant and is an intimate mixture of three individual constituents *viz*. curcumin (~94%), demethoxycurcumin (~ 6%) and bisdemethoxycurcumin (~0.3%). They are dicinnamoylmethane derivatives (Fig. 1) and are yellow-coloured substances. The economic significance of turmeric as a plant is almost entirely due to this curcuminoids constituent alone. For highly specialized requirements, pure curcumin (Curcumin I), the most important and abundant of the three constituents, is separated from the crude mix by column chromatography and is further purified on silica gel using chloroform/dichloromethane and ethanol/methanol mixtures as eluents. The commercially available turmeric based product 'Curcumin' or 'Curcumin C3 Complex' for use in culinary, cosmetics and pharmaceutical preparation is a mixture of curcumins I, II and III present to the extent of 80 to 90, 10 to 20 and 2 to 5%, respectively. According to Food Safety and Standards Authority of India (FSSAI), the curcuminoid content of commercial grade curcumin manufactured or sold as a food additive must not be less than 90% (dry weight basis). It may also be mentioned in the context that FSSAI prescribes the curcuminoid content of commercial grade turmeric powder for use as a kitchen spice to be not less than 2.0% (dry weight basis).

Functionally Active Constituents

Turmeric contains a wide range of substances. Of them, more than 250 distinctly different constituents have been isolated from its rhizome, and their chemical nature have been established. The biological and therapeutic functions of turmeric are however, confined to only three major classes of bioactive compounds *viz*. curcuminoids, essential oils and polysaccharides. Of the three, the curcuminoids which are the plant's secondary metabolites, like the alkaloids, flavonoids, and terpenoids, constitute the most significant class with regard to culinary and pharmacological value. Chemically, curcuminoids are substituted polyphenolic compounds with several functional groups, especially two keto groups outside the aromatic rings and joined by a methylene bridge. Curcuminoids are made of three individual bright yellow crystalline constituents *viz*. curcumin, demethoxycurcumin and bisdemethoxycurcumin, referred to also as curcumin I. II and III, respectively. Curcumin ($C_{21}H_{20}O_6$, molar mass 368.385 g mol^{-1}) is the most important of the three. Though first isolated in pure crystalline form from turmeric rhizome in 1815 by Henri Auguste Vogel and Pierre Joseph, its chemical structure was established almost a century later in 1910 by the Polish scientists Milobedzka and his two colleagues Lampe and Kostanecki. Its chemical name was assigned as diferuloylmethane [1,7-*Bis*(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Curcumin is a symmetrical molecule, and its structure possesses methoxy and hydroxy groups in identical positions of its two phenyl rings. The same group of workers later in 1913 accomplished the laboratory synthesis of curcumin. Curcumin exhibits two strong absorption bands – one in the visible range with λ_{max} at 415 to 420 nm and the other one in the far UV region with λ_{max} at 265 nm (both in methanol

solution). Demethoxycurcumin ($C_{20}H_{18}O_5$, molar mass 338.559 g mol^{-1}), similar in structure, lacks the methoxy group on one of the phenyl rings. Demethoxycurcumin [1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione] is thus not a symmetrical molecule. Bisdemethoxycurcumin ($C_{19}H_{16}O_4$, molar mass 308.333 g mol^{-1}) lacks methoxy groups on both the phenyl rings. Bisdemethoxycurcumin [1,7-*Bis*(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione] too is not a symmetrical molecule. Depending upon the cultivar, soil conditions and agronomic practices, the rhizome contains 2 to 9% curcuminoids of which curcumin alone accounts for more than 90%. Growers' choice for the cultivar and the market price of the rhizome depends on its curcumin content. Commercially available curcumin for its bulk use is a mix of the three of about 77, 17 and 3% along with a trace amount of cyclocurcumin, a newly found turmeric constituent. The essential oil, the second of the three major classes of bioactive compounds in turmeric, are all steam volatile, and responsible for the unique aroma, flavour and in part, the pharmacological significance of turmeric. They are made of a number of constituents *viz*. α- and β-turmerone, ar-turmerone, ar-curcumene, curlone, zingiberene, turmenorol A and B, α- phellandrene, borneol, sabinene, 1,8-cineole, and a number of sesquiterpenoids. Chemical structures of some of the characteristic constituents unique in the essential oil of turmeric are depicted in Fig. 2. Among the polysaccharides which constitute the third major class, important ones with therapeutic activity, especially antiviral and immunomodulatory properties, are curdilan and turmerin.

General Properties

Curcuminoids are brilliantly yellow-coloured crystalline solids, practically insoluble in water and acids, but soluble in organic solvents *e.g.* acetone, ethyl acetate, dimethyl sulfoxide and diethyl formamide. Water solubility is barely 3.5, 6.5 and 15 mg L^{-1} for curcumin, demethoxycurcumin and bisdemethoxycurcumin, respectively, pointing out the role played by the methoxy ($-OCH_3$) groups in hindering the formation of H-bonding with water molecules, thus contributing to a reduction in water solubility. Steric hindrance by the methoxy groups contributes to their melting points also. Efforts are on for curcumin's water soluble preparations by incorporation into surface active micellar systems *viz*. sodium dodecyl sulphate, polyethylene glycol, cyclodextrins, cetyl pyridinium bromide, and polysaccharides. However, the low water solubility (lipophilicity) helps curcumin in crossing the hydrophobic cell membranes at ease. The latter makes translocation of curcumin from cell to cell and organelle to organelle in biological systems an easy process. Curcuminoids are stable to light and relatively high temperature, a property that permits their use in making dishes and delicacies requiring heat treatment such as boiling, sauteing and deep frying.

Chemical Behaviour

Chemical behaviour of curcuminoids is determined largely by its four structural features *viz*. two substituted phenyl rings, hepta 1,6-diene-3,5-dione as a 7 C open chain linker acting as a bridge between the two phenyl rings, a methoxy (OCH_3) group attached to each of the two phenyl rings in 3-positions, and one hydroxy (OH) group attached to each phenyl ring in 4-positions (Fig. 1). The presence or absence of the methoxy ($-OCH_3$) groups forms the distinguishing structural feature among the three constituents of the curcuminoids. The methoxy groups are auxochromes and nonpolar electron donating entities capable of activating the aromatic rings and significantly influencing their physical and chemical properties *viz*. water solubility, polarity, melting point, acidity, antioxidant activity, and chemical reactivity. Curcumin is a tribasic weak Bronsted acid (H_3A) with three pK_a values of 7.8, 8.5 and 9.0 for the dissociation of the three acidic protons of the acid forming the weak bases H_2A^-, HA^{2-} and A^{3-}, respectively. The colour and the ionic form of curcumin changes with pH. At pH < 1, curcumin in aqueous solution exists in red coloured protonated H_4A^+ form; in the pH range of 1 to 7, most of it is water insoluble and exists in bright yellow coloured undissociated H_3A form; with further rise in pH, the nonionic form changes to red hued ionic forms of H_2A^-, HA^{2-} and A^{3-}. Curcumin is unstable in alkaline pH and degrades in about 30 minutes time to form a variety of degradation products. Under acidic pH, the degradation of curcumin is far slower. The two keto groups of a curcuminoid molecule make the structure a diketone. The latter in solution phase forms enols that are easily deprotonated to undergo typical keto enol tautomerism (Fig. 3). The enol form is more stable and abundant. The equilibrium of the keto enol tautomerism is strongly influenced by temperature, solvent system and pH. Under acidic to neutral pH, curcumin resorts to the keto form exhibiting chemical stability and acting as a proton donor (acid). At higher pH, curcumin gets unstable and shifts to the enol form, an electron donor that contributes to its antioxidant effects. The keto to enol ratio is a significant determinant factor of turmeric or curcumin's pharmacological properties. In dilute solutions with concentrations in μM range, 90% curcumin gets degraded in 30 min. The rate of degradation slows down with increase in concentration. Degradation proceeds through the α, β-unsaturated–β-diketo moiety. Important degradation products are *trans*-6(4$^{/}$-hydroxy-3$^{/}$-methoxyphenyl)-2,4-dioxo-3-hexenal (depicted as I), ferulic aldehyde, ferulic acid, feruloyl methane, vanillin, vanillic acid, and acetone (Fig. 4). When attached to lipids, liposomes, albumin, cyclodextrins, many macromolecular and micro heterogenous systems, the degradation rate is markedly reduced. This property is utilized in enhancing curcumin's bioavailability, a major deterrent in utilizing curcumin's medicinal potential. Curcumin undergoes photo degradation to form colourless products *viz*. vanillin, ferulic acid and substituted phenols. The other two constituents *viz*. demethoxycurcumin and bisdemethoxycurcumin also exhibit identical chemical behaviour and reactivity as described for curcumin, though however, to a lesser degree. In plant systems, the precursor for the biosynthesis of curcuminoids is L-phenylalanine, a primary metabolite and an essential amino acid. The common multistep pathway has different take-off points for the synthesis of any specific curcuminoid.

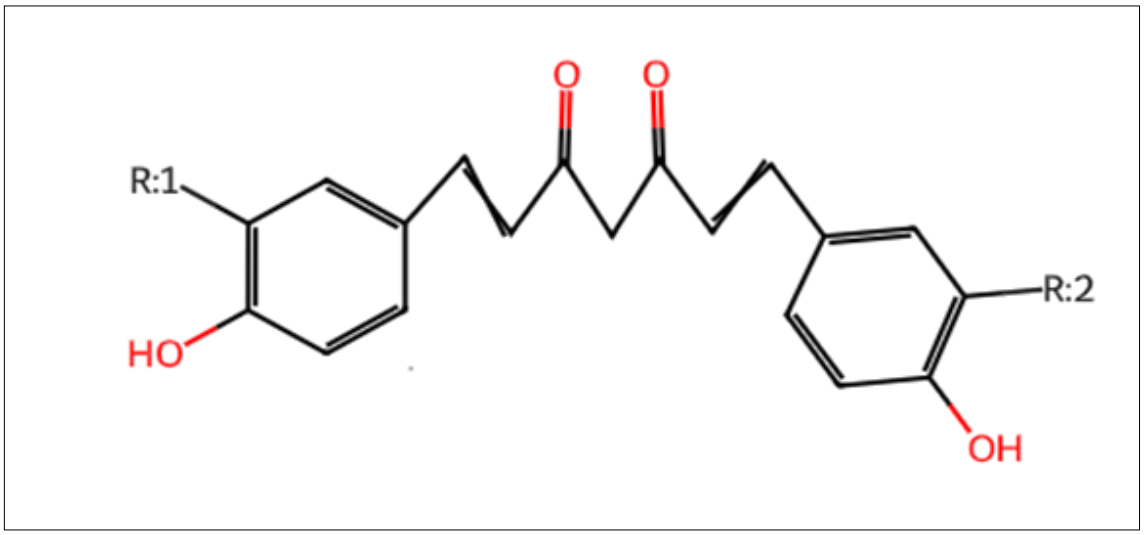
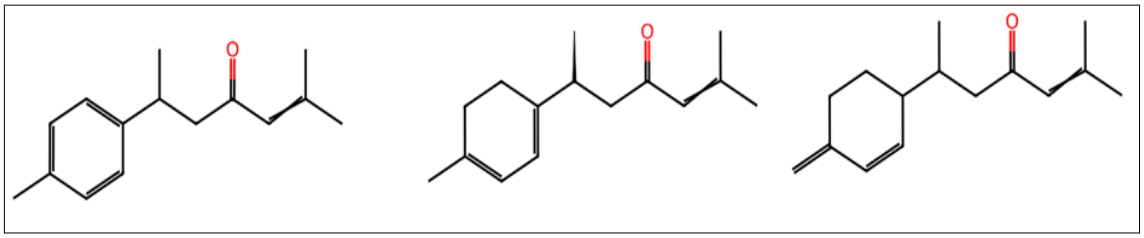
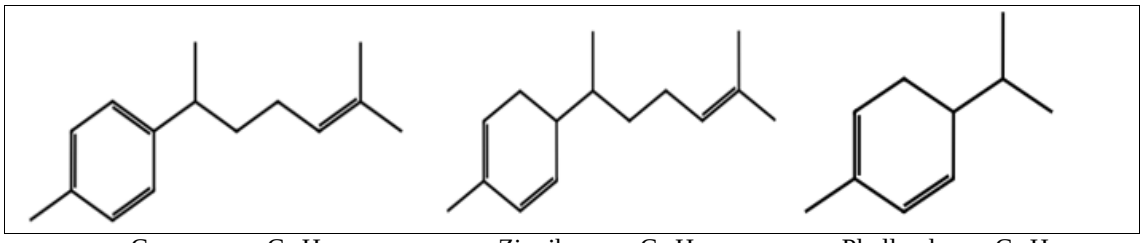


Fig 1: Chemical structure of curcuminoids. Curcumin, $R:_1 = R:_2 = -OCH_3$; demethoxycurcumin, $R:_1 = H$, $R:_2 = -OCH_3$; bisdemethoxycurcumin, $R:_1 = R:_2 = H$



ar-Turmerone. $C_{15}H_{20}O$ α- and β-Turmerone. $C_{15}H_{22}O$ Curlone. $C_{15}H_{22}O$



ar-Curcumene. $C_{15}H_{22}$ Zingiberene. $C_{15}H_{24}$ α-Phellandrene, $C_{10}H_{16}$

Fig 2: Major characteristic constituents of the essential oil of turmeric

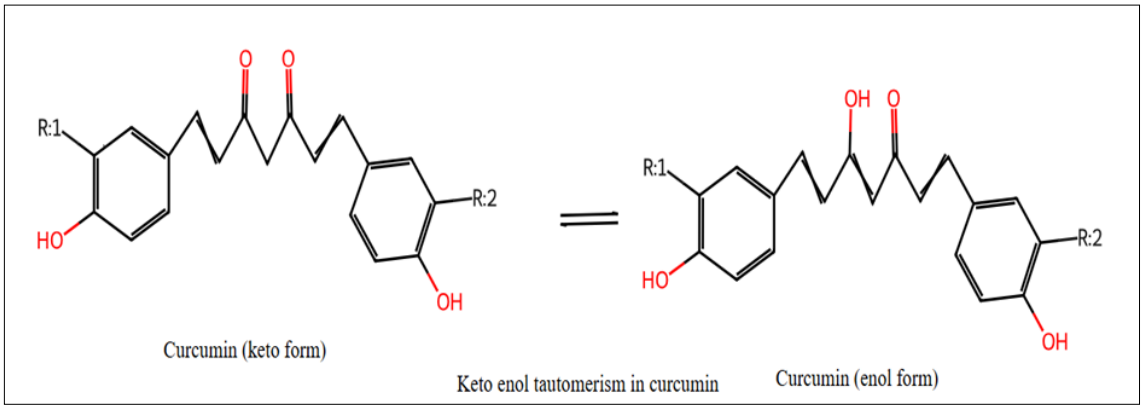


Fig 3: Keto enol tautomerism in curcuminoids. Curcumin, $R:_1 = R:_2 = -OCH_3$; demethoxycurcumin, $R:_1 = H$, $R:_2 = -OCH_3$; bisdemethoxycurcumin, $R:_1 = R:_2 = H$

Medicinal Properties

Despite modern medicines at the centre stage of health care, primarily for their 'quick action' results, plant-based naturals as their safer alternatives are not lagging much behind. Opting for the latter is due to their practically no adverse side effects, rapid elimination from the body and multiple target points with a concomitant broad spectrum of their therapeutic action. The awareness and rise in the use of plant based medicines is distinctly evident with turmeric. Use of turmeric, however, is no new to traditional Indian medicine and has been in use since ancient times. Applying a hot paste of turmeric with lime over the affected area of a

sprain or fracture or inflammation as a quick remedy is common in Indian homes. Far greater advantage of the medicinal use of curcumin, the master medicinal ingredient of the plant, lies in its being a highly pleiotropic molecule. Stated otherwise, it has multipoint targets and molecular sites of action. It does have properties that modulate the activity of many enzymes, growth factors, hormone receptors, signal molecules and chemical messengers, and other molecules. The net result is a wide range of pharmacological effects of turmeric. The latter includes among others anti-inflammatory, antioxidant and anti-cancer activities. Turmeric does have immunity boosting and antimicrobial property too and thus helps fighting infections by pathogens and parasites. Turmeric or curcumin thus proves useful in treating a wide ranging human diseases and disorders *viz*. biliary disorders, indigestion, hyperglycaemia, edema, hepatic disorders, urinary issues, sinusitis and wound healing.

Mode of Working

Chemical reactions associated with the biological activity of turmeric or curcuminoids are their H atom donation reactions leading to their getting oxidized, reversible and irreversible nucleophilic addition reactions, hydrolytic cleavage, degradation and a host of enzyme catalysed reactions. Their therapeutic activities are intimately related to the rates and directions of these chemical reactions. The antioxidant activity is attributed to its unique structural features *viz*. a carbon carbon double bond, β-diketo moiety and phenyl rings with hydroxy (OH) and methoxy (-OCH_3) groups. The molecule acts as a scavenger of a wide variety of Reactive Oxygen Species (ROS) *viz*. superoxide anion radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and nitrous oxide (NO) radicals, and does inhibit lipid peroxidation due to activation of different antioxidant enzymes such as super oxide dismutase (SOD), catalase and glutathione peroxidase. It inhibits also the activity of ROS generating enzymes such as cyclooxygenases (COX), lipoxygenases and xanthine dehydrogenase/oxidase. The molecule with its lipophilicity scavenges peroxy radicals too, much like vitamin E, another potent natural antioxidant. The order of antioxidant activity of the three curcuminoids is: curcumin > demethoxycurcumin > bisdemethoxycurcumin, due to the loss of electron donating -OCH_3 groups, reactivity of the conjugated double bond feature attached the phenyl rings, and chelation with heavy metal ions. For anti-inflammatory activity, the principal mechanism is inhibition of the COX-2 (cyclooxygenase-2) enzymes. Majority pain and inflammation types in human body follow the release of COX-2 mediators triggering the synthesis of prostaglandins. The latter cause pain, swelling and inflammation during physical injury and infection. Interference with the working of COX-2 finds support in the structural similarity of curcuminoids with celecoxib and etoricoxib (Fig. 5). The two are highly selective COX-2 inhibitors and nonsteroidal anti-inflammatory drugs (NSAID) used as pain relievers. The two NSAIDs have structural pharmacophore groups identical to curcuminoids *i.e.* a V-shaped molecule, two six membered rings (benzene rings for curcumin and celecoxib, and pyridine ring for etoricoxib), and a H-bond acceptor and donor. Regarding anti-inflammatory effectiveness, the three curcuminoids follow the same order as in the case of their antioxidant activity. For anti-cancer activity, the point of action is at multiple stages of the growth of the cancer cells. The activity begins with normal cells experiencing DNA damage due to exposure to physical, chemical and biological agents that can transform normal cells into cancer cells. At preventive stage, curcuminoid helps DNA repair by increasing the activity of the guardian genes, while decreasing the activity of cyclins, a class of regulatory proteins of cell cycles. At the curative stage, curcuminoids exhibit angiogenesis, a process of allowing cells to grow more aggressively, and anti-metastatis (preventing movement of cancer cells to nonaffected parts). In case of severe and irreparable DNA damage, curcuminoids act by enhancing pro-apoptotic and anti-cancer mediators. The order of anti-cancer activity of the three curcuminoids is the same as in the case of their antioxidant and anti-inflammatory property. Curcumin, a monobasic bidentate ligand, reacts with metal ions *viz*. Hg^{2+}, Pb^{2+}, Fe^{3+}, Ni^{2+}, Mn^{2+}, Cu^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+} etc. to form stable curcumin-metal ion complexes in 1:1, 2:1 (most common) and 3:1 stoichiometry (Fig. 6). These metal ion complexes alter the chemical reactivity, biological activity and toxicity of the metal ions, causing significant reduction in heavy metal toxicity caused by induced oxidative stress. Curcuminoid exhibits secondary antioxidant activity too through such chelation with transition heavy metal ions, thus preventing the latter from catalysing the formation of harmful free radicals. Further, some of these complexes bind to DNA, providing an early lead in utilizing this property in designing potent future antitumor agents. These metal ion complexes are attracting research interest also as diagnostic and clinical tools for Alzheimer's disease - a neurogenerative brain disorder affecting memory, thinking ability and behaviour - by reducing their oxidative damage. A great deal is expected from the research results of curcumin, its physico-chemically altered derivatives and its closely related synthetic analogues as high potential therapeutic agents for many chronic diseases, both at preventive and established stages.

Chemical structure-activity relationship studies of curcuminoids have shown that the two phenyl rings connected by the 7 C linker with keto enol tautomeric property are crucial for the biological activity of the molecule. Unsaturation in the 7 C linker provided by the conjugated double bonds provides conformational flexibility. The latter is of significance for its anticancer and antitumor properties. The phenolic OH, methoxy (-OCH_3) and CH_2 groups in the β-diketone moiety of the curcuminoid molecule confer anti-inflammatory and antioxidant properties, making it a valuable nutraceutical for chemopreventive and chemoprotective application. Fig. 7 depicts specific regions of the curcuminoid molecule conferring its antioxidant, anti-inflammatory, anticancer and metal binding property.

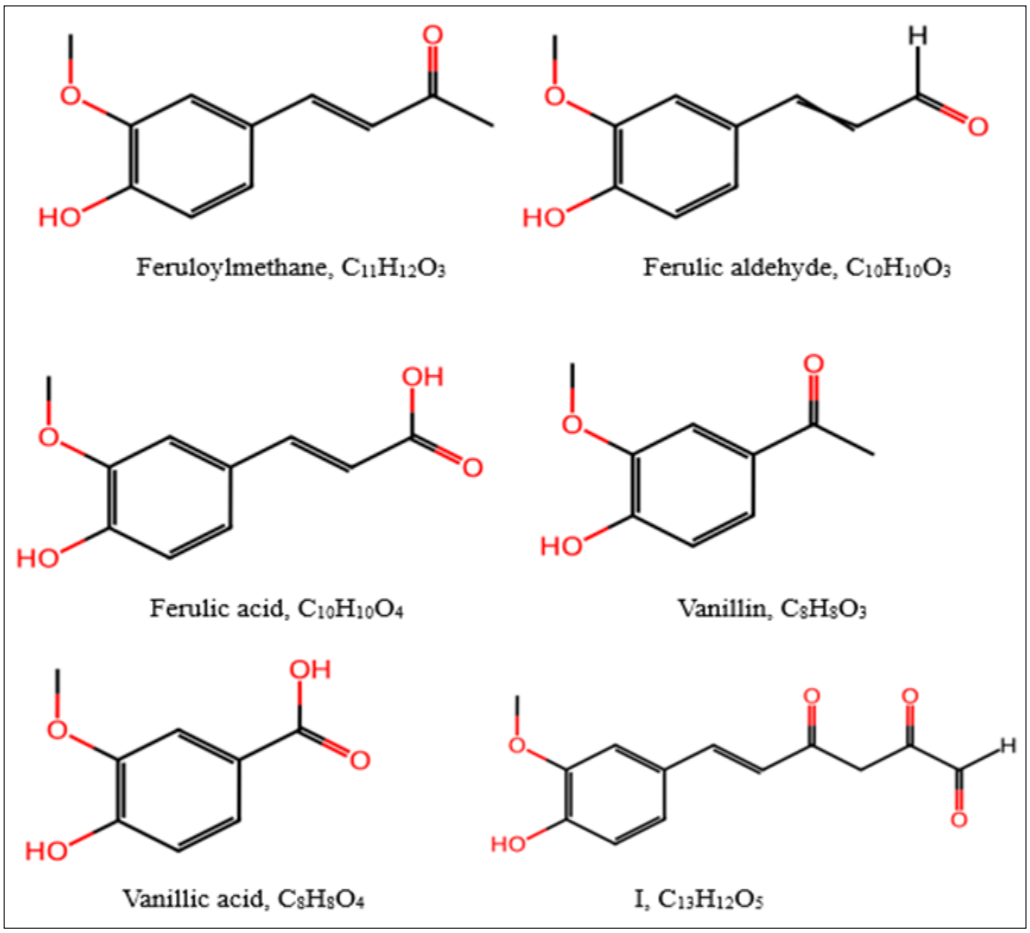


Fig 4: Major degradation products of curcumin

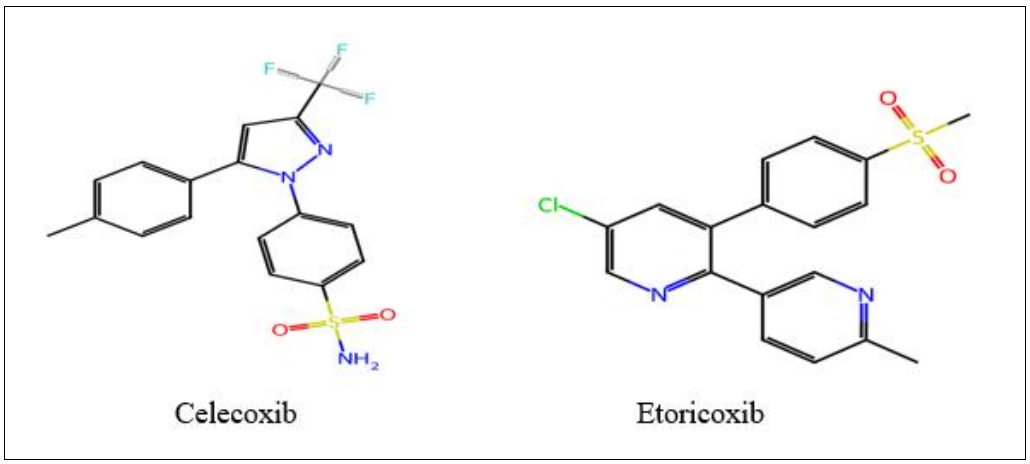


Fig 5: Celecoxib and etoricoxib molecules – structurally akin to curcuminoid

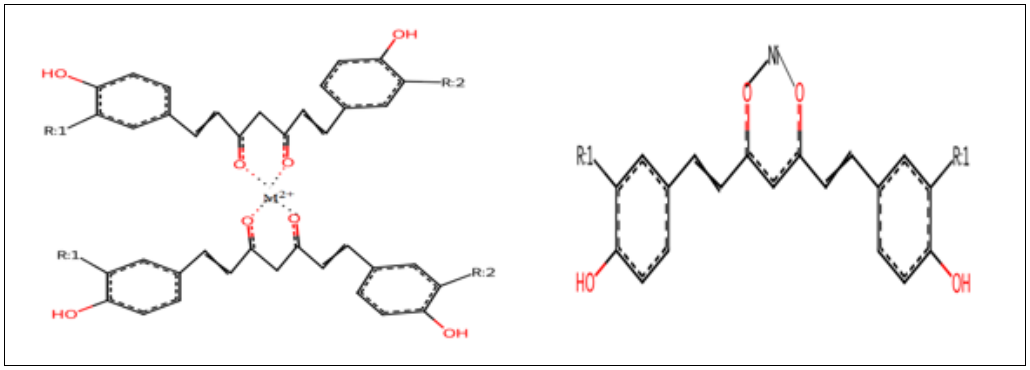


Fig 6: Curcumin-metal ion (divalent) complexes (2:1 with M^{2+} and 1:1 with Ni^{2+}).
$R:_1 = R:_2 = -OCH_3$

Metabolism

Only a small fraction of the turmeric or a curcuminoid ingested in human biological systems is absorbed in the gut. The left-over fraction gets excreted without any chemical change. The excretion is through faecal matter to the extent of as much as $\sim 95\%$, while only $\sim 1\%$ is eliminated through urine. Results revealed that 90 to 98% of the orally administered curcumin gets excreted out from the body through faeces and bile and the rest through urine. The less preference for elimination of a curcuminoid from the body through urine is due to its low water solubility. The small fraction that is absorbed undergoes a fast-paced metabolism in two distinct phases. In Phase I metabolism, cytochrome P450 or NADPH dependent reductases act upon the curcuminoids (C) to reduce it to di-, tetra-, hexa- and octa-hydro-curcuminoid (2 HC, 4 HC, 6 HC and 8 HC). Barring the 4 HC, the other three don't have any tangible biological activity in comparison to that of C. In Phase II metabolism, both the unaltered C and its reduced metabolites *viz*. 2 HC, 4 HC, 6 HC and 8 HC undergo conjugation with glucuronides and sulphates through OH groups of the former to form the corresponding β-D-glucuronide and β-D-glucuronide sulphate. Usually, glucuronide conjugates are twice more abundant than the glucuronide sulphate conjugates. These conjugates account for > 80% of curcumin metabolism. One primary factor contributing to the very low bioavailability of curcumin is the formation of these conjugates in the liver and intestine. The metabolic rate of the three curcuminoids (slowest to the fastest) is: curcumin > demethoxycurcumin > bisdemethoxycurcumin. The rate implies the hydrophobic -OCH_3 groups to exert a distinct role in shortening a curcuminoid's unaltered retention in the body, presumably by introducing steric hindrance. The latter delays glucuronic acid and sulphate conjugation. The $t_{1/2}$ (half-life) of curcumin is thus lower than that of the other two. The reasoning applies to their chemical degradation too. Of interest to mention is the point that majority of the metabolic products of a curcuminoid produced by enzyme catalysed reactions are different from its degradation products in isolated chemical systems. Some of the major products of curcumin metabolism are depicted in Fig. 8.

Poor Bioavailability - A Deterrent in Realising Turmeric's Therapeutic Potential

The bioavailability of curcuminoids is extremely low. Under average normal conditions, only about 2% of its pool is made available for it to act, a problem that seriously restricts realising the therapeutic potential of turmeric or curcuminoids for its use as medicinal agents. The poor bioavailability stems out primarily from three factors *viz*. poor intestinal absorption, rapid hepatic metabolism and fast systemic elimination from the body of whatever is left unmetabolized along with the major excretory products, *viz*. faeces, bile and urine. Curcuminoids do have a very short $t_{1/2}$ ($\sim$10 min for curcumin in a phosphate buffer in isolated chemical systems). The $t_{1/2}$ is very low in biological systems too ($\sim$ 90 to 120 minutes for curcumin). A curcuminoid thus does not receive much time to play its therapeutic role to its full potential. Enhancing curcuminoids' therapeutic potential thus requires a focus on prolonging their bioavailability in the body by increasing their $t_{1/2}$ and by reducing their rapid metabolism and elimination from the body. This in turn requires a two-pronged strategy. The first one is looking for the ways that inhibit curcuminoids' metabolic pathways leading to pharmacologically inactive metabolic products. The second one is honking those processes that slow down their rate of elimination from the body. A good number of strategies are in use or are in an experimental stage to overcome the problem of curcuminoids' low bioavailability. The simplest one is Combined Application with Adjuvants. This strategy involves co-administration with adjuvants such as piperine and lecithin. Both of them inhibit curcuminoids' metabolism and enhance their absorption. Piperine, an alkaloid present in black pepper and the most well-known substance in the context, inhibits enzymes involved in curcumin's metabolism, thereby increasing its systemic availability. Clinical trials revealed that such co-administration significantly increased curcumin level in the serum and its bioavailability increased as much as twenty times. Bromelain, a protein hydrolysing enzyme mix extracted from pineapple fruit and stem, is another such substance that can be co-administered. Bromelain increases a curcuminoid's absorption and anti-inflammatory activity. The co-administered agent added must however, not have any safety concern or any short- or long-term side effects in biological systems. Also, it must pass through the checks mandated by the statutory health authorities. The second strategy for increasing curcuminoids' bioavailability is Improving Delivery System Based on nanotechnology helping the molecule in reaching its target site of action very intelligently bypassing the 'on the way' obstacles. Liposomes, tiny artificial vesicles made of phospholipid bilayer, are used for encapsulating the molecules, facilitating their easier absorption and reaching the target site in an aqueous environment. Polymeric nanoparticles such as biocompatible synthetic polymers *e.g.* polyethylene glycol (PEG) and poly lactic-co-glycolic acid (PLGA) derivatives are used for such encapsulation. The latter improves their solubility and stability and in turn, enhances the kinetics of their release into the system and subsequent uptake and circulation time. Together they effect a rise in a curcuminoid's $t_{1/2}$ and raise its therapeutic effect. Mention may be made of polymeric micelles too. A curcuminoid, say curcumin, is solubilised within the hydrophobic core of the polymeric colloidal micelles formed from the added surface-active agents, thus increasing its bio-access and the concomitant bioavailability and bioactivity. Cyclodextrins are also in limited use for encapsulation. They are cone shaped cyclic oligosaccharides and form an outer complex with hydrophobic curcuminoids, duly improving their solubility and stability. The third strategy of much promise in increasing curcuminoids' bioavailability is the Prodrug Approaches. Such approaches require chemically modifying the molecule to overcome its undesirable properties *e.g.* water solubility, polarity, dielectric constant etc. This makes the prodrug entity permeable to membranes. The prodrugs remain chemically inert until metabolised to release the active curcuminoid present in the larger molecule just at the required target site. Curcumin chemically modified with various derivatives such as semicarbazone and oxime have

already been prepared. Many of them are highly bioavailable and bio effective. Some of them are potential anti-cancer agents too, thus opening a new research area for designing future anti-cancer agents. The fourth strategy for enhancing curcuminoids' bioavailability is Co-crystallization.

A curcuminoid, say curcumin for instance, is crystallized along with another compatible agent in a defined stoichiometric ratio. The added agent in no way alters the chemical structure or therapeutic behaviour of curcumin but increases its solubility and dissolution rate adding to its bioavailable pool in the serum.

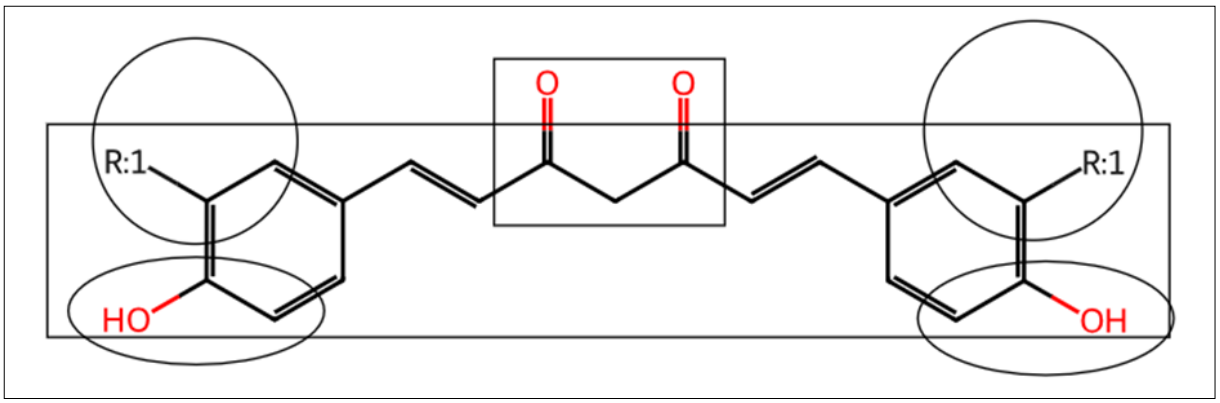


Fig 7: Regions in curcuminoid molecule responsible for different functional activities.
= Anticancer activity, = Antioxidant activity, = Chelation point, = Anti-inflammation.
Either one or both the two methoxy groups (R:1) are absent in demethoxycurcumin and bisdemethoxycurcumin, with a concomitant decline in activity.

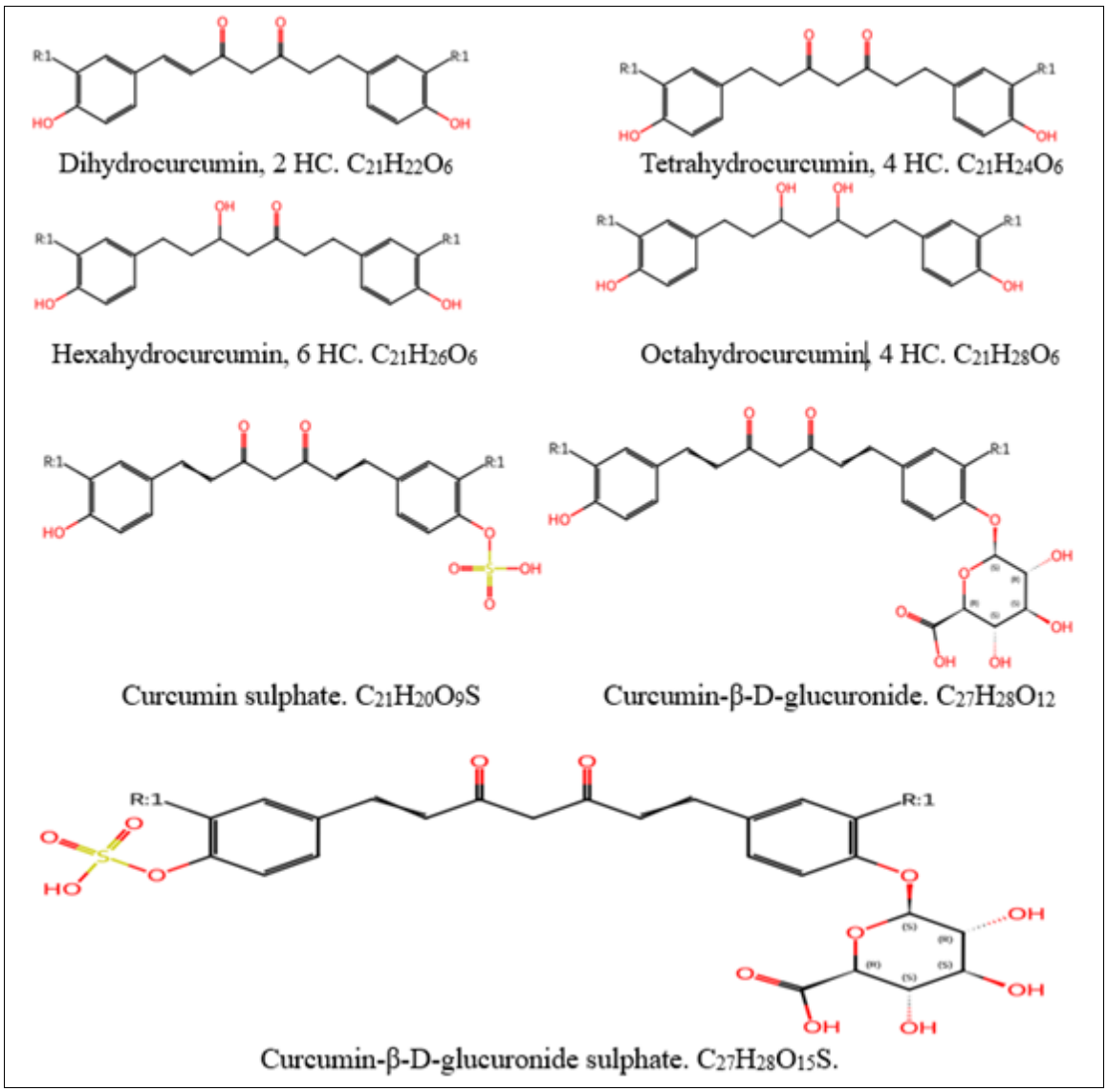


Fig 8: Principal metabolites of curcumin. R_1= -OCH_3

Side Effects

Turmeric or curcuminoids do have the great advantage of having practically no side effects or toxicity, even after long term use and that too at high dosages. Nevertheless, there are some isolated reports that at high dosages, they do cause few adverse effects. For instance, at dosages far higher than what is normally used, a curcuminoid has been reported to form complexes with soluble metal ions, notably iron, a process that causes iron deficiency leading to anaemia. There are few reports of their interaction with some functional proteins preventing the latter from exhibiting their biological activity such as enzyme activity or protective function. In few rare studies, curcuminoids have been found to be responsible for causing gastrointestinal issues such as nausea, stomach discomfort and abdominal distension. Also, there are also few reports indicating turmeric or a curcuminoid's blood clotting property and consequent interference with the working of blood thinning medications *e.g.* clopidogrel, aspirin and warfarin. However, all such effects are very mild, transient and rapidly disappear.

Conclusion

Turmeric is a traditional Indian plant with diverse uses *viz*. medicinal use for a range of ailments, culinary use for adding colour, flavour and aroma to the kitchen dishes, and use in textile industry as a yellow coloured dye. India is the world's largest turmeric producer and ranks first in export of its rhizome, the powder extracted from the rhizome, and a number of value-added products formed from the powder. The principal functional ingredient in turmeric is curcumin, an intense yellow crystalline solid. The functional activity and the market price of the rhizome are determined by its curcumin content. A major research area on turmeric should therefore be evolving hybrid turmeric varieties with high curcumin content. Curcumin apart, the two minor ingredients of economic significance in turmeric are demethoxycurcumin and bisdemethoxycurcumin. They are structurally similar polyphenolic substances present in the plant's rhizome. Curcuminoids are rapidly metabolised and eliminated from the body. Poor bioavailability of curcuminoids at the target site of action stands on the way of harnessing their therapeutic potential. Increasing the bioavailability of curcuminoid should thus be another important research area. Future research should focus also on synthetic structural variants of curcuminoid in search of novel drugs, potent enough to control various diseases and disorders.

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