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Review article

Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives – A review

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ABSTRACT

In recent years, several drugs have been developed deriving from traditional products and current drug research is actively investigating the possible therapeutic roles of many Ayruvedic and Traditional Indian medicinal therapies. Among those being investigated is Turmeric. Its most important active ingredient is curcuminoids. Curcuminoids are phenolic compounds commonly used as a spice, pigment and additive also utilized as a therapeutic agent used in several foods. Comprehensive research over the last century has revealed several important functions of curcuminoids. Various preclinical cell culture and animals studies suggest that curcuminoids have extensive biological activity as an antioxidant, neuroprotective, antitumor, anti-inflammatory, anti-acidogenic, radioprotective and arthritis. Different clinical trials also suggest a potential therapeutic role for curcuminoids in numerous chronic diseases such as colon cancer, lung cancer, breast cancer, inflammatory bowel diseases. The aim of this review is to summarize the chemistry, analog, metal complex, formulations of curcuminoids and their biological activities.

1. Introduction

Natural products have been used in traditional medicines for thousands of years, and have shown promise as a source of components for the development of new drugs.[1,2] Turmeric (*Curcuma longa Linn*) is a member of the *Zingiberaceae* family and is cultivated in tropical and subtropical regions around the world and it is originates from India, Southeast Asia and Indonesia.[3] Turmeric powder is used extensively as a coloring and flavoring agent in curries and mustards. Turmeric has been used in India to maintain oral hygiene.[4] It has traditionally been used for medical purposes for many centuries in countries such as India and China for treatment of jaundice and other liver ailments.[5,6] Turmeric is one of the most popular medicinal herbs, with a wide range of pharmacological activities such as antioxidant,[7] anti-protozoal,[8] anti-venom activities,[9] anti-microbial,[10] anti-malarial,[11] anti-inflammatory,[12] anti-proliferative,[13] anti-angiogenic,[14] anti-tumor[15] and anti-aging[16] properties. It has also been used to treat ulcers, parasitic infections, various skin diseases, anti-immune diseases and curing the symptoms of colds and flus.[17] The pharmacological activity of turmeric has been attributed mainly to curcuminoids consists of curcumin (CUR) and two related compounds demethoxy curcumin (DMC) and bisdemethoxycurcumin (BDMC).[3] CUR itself appears as a crystalline compound with a bright orange-yellow color. Curcuminoids are commonly used as coloring agent as well as food additives. World Health Organization (WHO) stated the acceptable daily intake of curcuminoids as a food additive in the range of 0–3 mg/kg. Curcuminoids and turmeric products have been characterized as safe by the Food and Drug Administration (FDA) in USA. The average intake of turmeric in the Indian diet is approximately 2–2.5 g for a 60 kg individual which corresponds to a daily intake of approximately 60–100 mg of CUR.[18] Curcuminoids have achieved the potential therapeutic interest to cure immune related, metabolic diseases and cancer due to a vast number of biological targets and virtually no side effects.[17,18]

2. Methodology

Systemic literature searches were carried out using following databases; Pubmed, Scifinder, Scopus, ScienceDirect, Medline, Embase, Google Scholar and Web of Science using the key words,

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turmeric, *C. longa*, curcuminoids, curcumin, bioavailability, bioenhancer, pharmacokinetic, phytosome, liposome, analogs, metal complexes and nanoparticles (NPs) and a library search for articles published in peer-reviewed journals and also locally available books.

3. Discovery of curcumin

Curcumin is the active ingredient of the dietary spice turmeric and is extracted from the rhizomes of *C. longa*, a plant in the *Zingiberaceae* family. It was first discovered about two centuries ago when Vogel and Pelletier reported the isolation of a “yellow coloring matter” from rhizomes of *C. longa* and named it curcumin.[19] It is characterized by Milobedeska et al[20] and first synthesized by Lampe et al.[21]

4. Isolation of curcumin

Curcumin is insoluble in water; an organic solvent has been used for its isolation. Anderson et al[22] developed a technique for isolating CUR from ground turmeric. They magnetically stirred the ground turmeric in dichloromethane and heated at reflux for 1 h. The mixture was suction-filtered, and the filtrate was concentrated in a hot-water bath maintaining at 50 °C. The reddish-yellow oil residue was triturated with hexane and the resulting solid was collected by suction filtration. Further TLC analysis (3% methanol and 97% dichloromethane) showed the presence of all three components.[22] Bagchi[23] explained extraction of CUR from turmeric powder with the use of a solvent consisting of a mixture of ethanol and acetone. Chemical analyses have shown that turmeric contains carbohydrates (69.4%), moisture (13.1%), protein (6.3%), fat (5.1%) and minerals (3.5%). The essential oil (5.8%) obtained by steam distillation of the rhizomes contains α-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%), curcumin (3–6%) is responsible for the yellow color.

5. Physical, chemical and molecular properties of curcuminoids

Two active components of turmeric are the volatile oil and curcuminoids and both are present in oleoresin extracted from the turmeric root. The essential oils are composed mainly of sesquiterpenes, many of which are specific for the Curcuma genus. The aroma of this spice is principally derived from α- and β-turmerones and aromatic turmerone (Ar-turmerone).[24] The chemical structures of curcuminoids make them much less soluble in water at acidic and neutral pH, but soluble in methanol, ethanol, dimethyl sulfoxide and acetone. The curcuminoids give a yellow-orange coloration to turmeric powder due to the wide electronic delocalization inside the molecules that exhibit strong absorption between 420 to 430 nm in an organic solvent. The curcuminoids are a mixture of curcumin, chemically a diferuloylmethane [1,7-bis(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione] mixed with its two derivatives, demethoxy curcumin [4-hydroxycinnamoyl-(4-hydroxy-3-methoxycinnamoyl) methane] and bis-demethoxy curcumin [bis-(4-hydroxy cinnamoyl) methane], defining the chemical formulae as $C_{21}H_{20}O_6$, $C_{20}H_{18}O_5$ and $C_{19}H_{16}O_4$ respectively.[17] The chemical structures of important constituents present in turmeric are given in Fig. 1. They share the same structure with two benzenemethoxy rings, joined by an unsaturated chain. It has three important functions: an aromatic methoxy phenolic group; α,β-unsaturated β-diketo linker and keto-enol tautomerism. All these compounds exist in the trans-trans keto-enol form. The aromatic groups provide hydrophobicity and the linker give flexibility. The tautomeric structures also influence the hydrophobicity and polarity. The hydrophobicity of curcuminoids makes them poorly soluble in water. Three acidity constants (pKa) were measured for curcuminoids as follows, pKa1 = 8.38 ± 0.04, pKa2 = 9.88 ± 0.02 and pKa3 = 10.51 ± 0.01.[25] Typical curcuminoids composition of popular Indian varieties was found to be in the range of CUR 52–63%, DMC 19–27% and BDMC 18–28%.[17]

The aim of this review was to overview the biological activities of curcuminoids and other biomolecules from turmeric and also discussed the effects and applications of curcuminoids and its different types of derivatives.

6. Biological activities of curcuminoids

Curcuminoids from turmeric and their derivatives have been shown to possess a wide range of biological activities including antioxidant, anti-inflammatory, anticancer, antimicrobial, neuroprotective, cardioprotective and radioprotective effects etc., and are illustrated in Fig. 2. The potential of curcuminoids in various biological activities involving multiple mechanisms is given in Table 1 and Fig. 3.

6.1. Neuroprotective effects and medicinal use in Alzheimer's disease (AD)

The pathogenesis of neurodegenerative diseases such as Alzheimer or Parkinson is multi-factorial with a complex combination of genetic components and environmental factors. Toxic reactions, including inflammation, glutamatergic toxicity, dysfunction of mitochondrial activity and ubiquitin/proteasome system, the activation of apoptosis pathways, the elevation of iron and nitric oxide and the alteration of the homeostasis of antioxidants/oxidation are involved in the pathogenesis of neurodegenerative diseases.[26] Dohare et al[27] explained the mechanisms of the neuroprotection against experimental cerebral ischemia by curcuma oil isolated from the rhizomes of *C. longa*. Curcuma oil suppressed the rise in the intracellular concentration of Ca^{2+}-a common component in the signaling pathways. The high levels of NO generated by NOS isoforms that are partially responsible for exacerbating the neuronal damage were reduced by curcuma oil. Curcuma oil prevented post-ischemic brain neutrophil infiltration and NO metabolites and reduced the production of ROS. Curcuma oil suppressed the elevated protein level of Bax, and the mitochondrial translocation and activation of Bcl-2 that is triggered by altering mitochondrial membrane potential. Curcuma oil exerted its major action in the penumbral region of the infarct that is protected by modulation of apoptosis. The neuroprotective effect was due to the reduction of NO-induced formation of peroxynitrite and apoptosis in the transient MCAo model in rat. Dohare et al[28] also studied on CUR administrated at various dose levels after 4 h of clot implant in the rat embolic stroke model. The rats were scored at 24 h after surgery for neurological dysfunction, locomotor activity and motor coordination test, infarct volume, edema volume, brain tissue nitrate/nitrite, myeloperoxidase, GSH and GSH-Px activity. The flow cytometric estimation in neuronal rich cell population the level of ROS, NO and peroxynitrite generation were studied at 24 h, which contributed to serve neuronal cytotoxicity were selectively inhibited by CUR treatment. Ischemia induced increase in brain infarct volume and edema volume were significantly attenuated by CUR treatment. The neurobehavioral assessment, locomotor activity and motor coordination further strengthen the above biochemical data there by indicating neuroprotective effect of CUR administrated at 4 h after ischemia in rat focal embolic stroke model. Sahoo et al[29] investigated the effect of CUR on oxidative stress parameters such as antioxidant defense enzymes and oxidized (GSSG) and reduced glutathione (GSH) levels in testis of L-thyroxine (T4)-induced