Review / Derleme

Antioxidant and Anticancer effects of curcumin – A Review

Zerdeçalın Antioksidan ve Antikanser Etkileri – Derleme

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ABTRACT

Plants are nature's remedies & have been used on earth for food and medicine since ancient times. The use of plants and their active principles in the prevention and treatment of chronic diseases is on the experience of traditional system of medicine from different ethnic societies but use in modern medicines is limited by the lack of scientific data. Few medicinal plants have attracted the interest & been the subject of scientific investigations,One plant that has been investigated is turmeric. Turmeric and its active ingredient "curcumin''are being studied upon as chemopreventive agents in various diseases.Curcumin has a long history of use in ayurvedic medicine as a treatment for inflammatory conditions.The medicinal properties of curcumin and its analogs have been known to mankind for ages.Modern science has now provided a scientific basis to the numerous reports of the medicinal effects of these most inexpensive,yet pharmacologically safe, having numerous pharmacological activities, including antioxidant and antimicrobial properties.This review article focuses on curcumin's anti-inflammatory,antioxidant and anticancer properties and its role in premalignat conditions of oral cavity.

Key words: Curcumin, turmeric, antioxidant

Introduction

Plants have been a major source of medicine since the ancient time. Natural plant products have been used throughout human history for various purposes. Among natural origin polyphenols appear as one of the most important group[1]. These polyphenols have recently received much attention in disease prevention and treatment due to their antioxidant properties.[2]Among polyphenols, Curcumin is one of the most studied substances. It is hydrophobic, low molecular weight polyphhenol widely used in the form of spice, turmeric.[3]Haridra or Curcuma longa Linn, commonly known as turmeric has been used for centuries as a spice and household remedy. In Ayurveda its use has also been recommended for various medical indications like wound healing, nausea, indigestion, inflammation, liver diseases, improving skin complexion etc.[4]

The turmeric (Curcuma longa) plant, a perennial herb belonging to the ginger family, is cultivated extensively in south and southeast tropical Asia. The rhizome of this plant is also referred to as the "root" and is the most useful part of the plant for culinary and medicinal purposes. The most active component of turmeric is curcumin, which makes up 2–5% of the spice. The characteristic yellow color of turmeric is due to the curcuminoids, Curcumin is an orange-yellow crystalline powder practically insoluble in water.[5]

Curcuma extracts contain three diarylheptanoids namely, curcumin as the major component together with smaller amounts of demethoxycurcumin and bis-demethoxycurcumin.curcuminoids have a unique conjugated structure including a β -diketone moiety due to which they undergo keto-enol tautomerization and exist entirely in the enol form in solution.[6] The curcuminoid complex is also known as Indian saffron. Curcumin is a lipophilic polyphenol that is nearly insoluble in water but is quite stable in the acidic pH of the stomach.[7]

Ayurveda, Unani, Siddha and Chinese medicines recommend curcumin for a wide range of disorders and diseases. Modern science has provided a scientific basis for such uses. Curcumin has been shown to be a very powerful antioxidant more potent than tocopherols, a comprehensive anti-inflammatory, and an anticancer compound beneficial in virtually all forms of human cancers, including cancers refractory to common anticancer drugs.[8]Curcumin contains two para hydroxyl groups, two keto groups,two methoxy groups, an active methylene group and two double bonds. The presence of hydroxyl groups on phenyl ring is responsible for antioxidant activity of curcumin. The presence of keto groups & double bonds is essential for anti-anti inflammatory, anticancer activities.[5]

HISTORY

The medicinal history of turmeric is at least 2500 years old. Ayurveda, Unani, Siddha and Chinese medicine recommend turmeric for a large number of disorders and diseases. Susruta's Ayurvedic Compendium, dating to 250 BC, recommends an ointment containing turmeric to relieve the effects of poisoned food. Turmeric is highly esteemed by the Indians & has a religious importance because of its yellow color resembling sunlight. Turmeric is used as aromatic spices & when added to various food preparations preserved their freshness& nutritive value, act as a antiseptic agent. Traditionally in indian turmeric is used in various cuisines for flavour, as an additive (spice), preservative and colouring agent. Turmeric has always been considered an auspicious material in the indian sub-continent. Yellow and yellow-orange are colors with sacred and auspicious connotations in India, yellow being associated with Vishnu, and as the color of the space between chastity and sensuality.

Turmeric also is a highly valued cosmetic ingredient. Oil bath routines with the application of Haldi are almost sacrosanct with the South Indian women, resulting in beautiful skin, and hairless bodies. Pieces of the rhizomes are added to water to make an infusion that is used in baths. It is reported that washing in turmeric improves skin tone and reduces hair growth. Turmeric is currently used in the formulation of some sun screens.

Traditional Indian medicine use the powder against billary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatic disorders, sprains and swellings caused by injury, and sinusitis. Externally, the dried rhizome has been applied to fresh wounds and to insect stings and to help the healing process in chickenpox and smallpox. It is also applied topically for ulcers, wounds, eczema, and inflammations. In both the Ayurvedic and Siddha systems of medicine, a turmeric paste is used topically to treat ulcers and scabies. The Himalayan system of medicine recommends turmeric for contraception, swelling, insect stings, wounds, whooping cough, inflammation, internal injuries, pimples, injuries, and as a skin tonic

Turmeric was mentioned in the writings of Marco Polo concerning his 1280 journey to China and India and it was first introduced to Europe in the 13thcentury by Arab traders. Although Vasco de Gama during 15th century, after his visit to India, truly introduced spices to the West, it was during the rule of British in India that turmeric was combined with various other spices and renamed "curry powder," as it is called in the West.

MECHANISM OF ACTION

Anti-inflammatory actions: Anti-inflammatory mechanisms curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of the inflammatory cytokines tumour necrosis factor-alpha (TNF-a), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinases.[9,10]

COX-2 and iNOS inhibition are likely accomplished via curcumin's suppression of nuclear factor kappaB (NF-κB) activation. [11]NF-κB, a ubiquitous eukaryotic transcription factor, is involved in regulation of inflammation, cellular proliferation, transformation, and tumorigenesis. Curcumin is thought to suppress NF-κB activation and proinflammatory gene expression by blocking phosphorylation of inhibitory factor I-kappa B kinase (IκB). Suppression of NF-κB activation subsequently down-regulates COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis. [11,12]

Curcumin's inhibition of inflammatory cytokines is through a number of mechanisms. In vitro studies indicate curcumin regulates activation of certain transcription factors such as activating protein-1 (AP-1) and NF-κB in stimulated monocytes and alveolar macrophages, thereby blocking expression of cytokine gene expression. Down-regulation of intercellular signaling proteins, such as protein kinase C, in which curcumin inhibits cytokine production.[7]

Antioxidant property: The antioxidant activity of curcumin depends upon the presence of both the central methylene hydrogens and the phenolic hydrogens, are involved in the mechanism of formation of the phenoxy radicals. It has a conjugated structure & shows a typical radical trapping ability as a chain breaking antioxidant properties. Generally, it has dual effect in oxygen radical reactions, thus it can act as a scavenger of hydroxyl radicals or it catalyses the formation of hydroxyl radicals.The antioxidant activity of curcumin could be mediated through antioxidant enzymes such as superoxide dismutase, catalases & gluthaione peroxidase.

The antioxidant mechanism of curcumin may involve one or more of the following interactions:

- scavenging or neutralizing of free radicals
- inhibition of oxidative enzymes
- oxygen quenching and making it less available for oxidative reactions
- interacting with oxidative cascade & preventing its outcome
- chelating or disarming oxidative properties of metal ions like iron. [5]

It can protect haemoglobin from oxidation.[13] In vitro, curcumin can significantly inhibit the generation of reactive oxygen species (ROS) like superoxide anions, hydrogen peroxide and nitrite radical generation by activated macrophages, which play an important role in inflammation.[14]Curcumin also lowers the production of ROS in vivo. Its derivatives, demethoxycurcumin and bis-demethoxycurcumin also have antioxidant effect.[15] Curcumin exerts powerful inhibitory effect against hydrogen peroxide -induced damage in human keratinocytes and fibroblasts [16] and in NG 108-15 cells.[17]It also decreases lipid peroxidation in rat liver microsomes, erythrocyte membranes and brain homogenates. This is brought about by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase.In fact, curcumin has been found to be atleast 10 times more active as an antioxidant than even vitamin E.[18] Curcumin has been shown to serve as a Michael acceptor reacting with glutathione and thioredoxin 1.5 Reaction of curcumin with these agents reduces intracellular GSH in the cells. [19]The antioxidant mechanism of curcumin is attributed to its unique conjugated structure, which includes two methoxylated phenols and an enol form of b-diketone.So the curcumin effectively inhibit the free radical damage to biomolecules by prevention & intervention processes which makes it very unique natural antioxidant.[20]

Anticancer activity: Curcumin is an important anticancer agent & it decreases the cancer initiation of skin, mammary gland, oral cavity, esophagus. The curcumin induces the apoptosis in

various cancerous cells, therefore it has an ability for cancer therapy. It causes suppression of inflammation, inhibition of cell proliferation, suppression of certain oncogens, inhibition of transcription factors NF-KB & ap-1 suppressions of COX-2, inhibition of chromosomal damage, inhibition of tumor implantation, inhibition of tyrosine kinase c activity, inhibition of biotransformation of carcinogenesis& induction of gluthione s transferase activity.[5]

Radio sensitization and radioprotection: An interesting aspect of curcumins activity is the ability to exert both radioprotective effects in normal cells and radiosensitizing effects in cancer cells. [21]Although the mechanisms enabling curcumin to exerts these opposing effects are not entirely understood, it has been suggested that curcumins ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress and inflammatory responses may afford protection against the harmful effects of radiation, whereas the radiosensitizing activity might be due the upregulation of genes responsible for cell death. Radiation induces pro-survival factors such as increased NF-Kb activity and up-regulation of Bcl-2 in PC3 cells; however, curcumin treatment in combination with radiation showed inhibition of TNF-a-mediated NF-kB activity, resulting in down-regulation of Bcl-2. [22]

Effect of curcumin on the tumor microenvironment: Inhibition of angiogenesis and metastasis: Angiogenesis, a fundamental process by which new blood vessels are formed from existing vessels, is essential in reproduction, development, and wound repair. Tumor growth and metastasis are dependent upon the formation of new blood vessels to sustain growth and to allow tumor cells to enter the circulation and metastasize to distant sites.Curcumin has been shown to interfere with many of the processes involved in angiogenesis .[23] Studies demonstrated that curcumin inhibits fibroblast growth factor (FGF) induced neovascularization. [24,25] The angiogenic ligands vascular endothelial growth factor (VEGF) and angiopoietin 1 and 2,which act in a coordinated fashion in angiogenesis, were inhibited by curcumin in Ehrlich ascites tumor (EAT) cells, and VEGF and angiopoietin1 gene expression were inhibited. Curcumin had an inhibitory effect (in vitro) on the angiogenic receptor kinase-insert domain receptor (KDR) on human umbilical vein endothelial cells (HUVECs). Additional effects of curcumin on angiogenesis and metastasis may be mediated by its ability to regulate cell adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (ELAM-1), cell surface proteins involved in tumor metastasis. Thus, curcumin completely blocked the adhesion of monocytes to endothelial cells as well as the cell surface expression of ICAM-1, VCAM-1, and ELAM 1. [22]

Effects of curcumin on tumor suppressor p53: The tumor suppressor and transcription factor p53 is a critical regulator in many cellular processes including cell signal transduction, cellular response to DNA damage, genomic stability, cell cycle control, and apoptosis. [26]p53 which mediates apoptosis under many stress conditions, and its downstream targets p21waf1/cip1 and growth arrest and DNA damage inducible gene 45, are over expressed during curcumin-induced apoptosis in a human basal cell carcinoma and p53 and c-myc were up-regulated in a human hepatoblastoma cell line after curcumin treatment.Curcumin was found to up-regulate cyclin-dependent kinase inhibitors (CDKIs),p21WAF1/CIP1, p27KIP1, and p53 in immortalized HUVECs.[27] Curcumin caused the growth arrest and apoptosis of BKS-2immature B cell lymphoma by down-regulation of growth and survival promoting genes (egr-1, c-myc,Bcl-XL, and NF-kB) as well as p53.

Antimicrobial activity: Curcumin inhibits the growth of varieties of microbes such as viruses, bacteria & some pathogenic fungi[7].Turmeric act as an antiviral agent against human immunodeficiency virus & curcumin inhibits the activation of long terminal repeat, which is the essential part of common system in HIV& decreases the replication of human immunodeficiency virus.[28]

BIOAVAILABILITY AND PHARMACOKINETICS:

Various studies have shown the biotransformation of curcumin. It was first biotransformed to dihydrocurcumin and tetrahydrocurcumin, these compounds were than subsequently converted to monoglucuronide conjugates. [29]Thus the major metabolites of curcumin are curcumin-glucuronide, dihydrocurcumin glucuronide, tetrahydrocurcumin-glucuronide and tetrahydrocurcumin. Biotransformation of curcumin occurs mainly in the liver, although some metabolism occurs in the kidney and gastrointestinal tract. [1]

Curcumin has poor bioavailability due to its rapid metabolism in the liver and intestinal wall. Curcumin bioavailability can be increased by administration of piperine, a known inhibitor of

hepatic and intestinal glucuronidation. Piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in humans. [30]

ABSORPTION OF CURCUMIN

The pharmacokinetic properties of curcumin in humans remain relatively unexplored. In rodents, curcumin undergoes avid metabolism by conjugation and reduction, and its disposition after oral dosing is characterized by poor systemic bioavailability. In a pilot study of a standardized oral curcuma extract, doses up to 180 mg of curcumin per day were administered to patients with advanced colorectal cancer for up to 4 months without overt toxicity or detectable systemic bioavailability. [31]

A phase I clinical trial conducted on 25 patients with various precancerous lesions demonstrated oral doses of 4, 6, and 8 g curcumin daily for three months yielded serum curcumin concentrations of only 0.51 ± 0.11, 0.63 ± 0.06, and 1.77 ± 1.87 μM, respectively, indicating curcumin is poorly absorbed and may have limited systemic bioavailability.[7]

DOSE

Curcumin is well tolerated, but its bioavailability is poor. It does not appear to be toxic to animals or humans even at high doses. Cheng et al [32]conducted a Phase I trial of curcumin in patients with high risk or premalignant lesions in Taiwan; 24 patients completed the study. Patients included those with resected bladder cancer, oral leukoplakia, stomach metaplasia, cervical intraepithelial neoplasm and Bowens disease. Curcumin was administered as a single daily oral dose ranging from 500 to 8000 mg/day for 3 months. No toxicity was observed at any dose. Pharmacokinetic studies were performed in patients receiving 4000 – 8000 mg/day. Serum concentration peaked 1 –2 h after oral intake and then gradually declined. Maximum serum concentration ranged from 0.50.11 μM at 4000 mg/day to 1.771.87 μM at 8000 mg/day. At lower doses, curcumin was not detectable in serum. Pharmacokinetic parameters remained the same after patients had taken curcumin for 1 month. Curcumin was not detected in the urine. [22]

Curcumin appears to be safe in both large and small animal models, but few systematic studies of curcumin's pharmacology and toxicology in humans have been performed. Minimal toxicity of doses up to 8,000 mg have been described in humans and to date, no maximum tolerated dose has been defined. The tolerance of curcumin in single oral doses up to 12,000 mg appears to be excellent.Despite curcumin's apparent poor bioavailability peak plasma concentration has been identified 1 to 2 hours after single dose oral administration of 4,000 mg and higher.[33]

A study has suggested that doses up to 8 g could be administered daily to patients with premalignant lesions for 3 months without overt toxicity .[32]

Studies in healthy human volunteers consuming a single dose of curcumin ranging from 500 to 12 000 mg gave a similar overall picture. No dose-limiting toxicities were observed, and low levels of curcumin were only detected in the serum receiving the highest doses of curcumin (10 000 or 12 000 mg/day). [33]

SIDE EFFECTS

Curcumin is considered to have a low toxicity in man and animals. In a clinical trial with 25 volunteers, administration of up to 8 gm of curcumin per day has no apparent toxic sign. There are no reports of adverse effects of either curcumin or its analogues except for rare cases of contact dermatitis. Contact dermatitis has been reported with occupational exposure and a small number of patients using turmeric topically reported pruritis at the site. In another study, 8% of patients taking 1 g oral turmeric for dyspepsia reported nausea. Oral administration of curcumin to rats at doses up to 5 g/kg caused no overt signs of toxicity. The American Herbal Association classifies curcumin as a menstrual stimulant and some sources recommended avoiding Curcumin in pregnancy.

Curcumin may have an antiplatelet activity and its concurrent use with anticoagulants may lead to an additive effect. Although there are no reports of this in humans, its use should be avoided in patients with bleeding disorders and bile duct. Oral curcumin has been associated with gallbladder contraction in humans over a two-hour period after administration of a single 20 mg dose. Therefore, curcumin use may be inadvisable in patients with cholelithiasis obstruction and should only be used under the supervision of a physician in patients with gallstones.

In animal studies, curcumin was shown to induce abnormalities in liver function tests. In human studies, 750 mg of turmeric twice daily for

30 days did not change liver function tests, the same result was reported using 20 mg of curcumin for 60 days.

PRECAUTIONS

Curcumin should be avoided in patients allergic yellow food colorings, or other members of the Zingiberaceae (ginger) family. It should be avoided in patients with bile duct obstruction or cholelithiasis, and gastric or duodenal ulcers or other hyperacidity disorders.. curcuminshould not be taken in large amounts during pregnancy as it might stimulate menstrual flow and uterine contraction. Animal studies have not shown any teratogenicity. There is insufficient evidence of safety to support use of large amounts of curcumin during lactation.

ROUTES OF ADMINISTRATION

Curcumin has been used for various purposes and through different routes of administration. It has been used topically on the skin for wounds, blistering diseases such as pemphigus and herpes zoster, for parasitic skin infections, chicken pox, small pox and for acne.

It has been used via oral administration for the common cold, liver diseases, urinary tract diseases, and as a blood purifier. It has been used via inhalation for chronic rhinitis and coryza. [35]

AVAILABLE FORMS:	RECOMMENDED DOSE:
• Capsules containing powder(Tab haridra 400mg) • Fluid extract • Turmeric oil • Tincture • Gel (Curenext oral gel)	• Cut root:1.5-3g per day • Dried ,powder 1-3 g per day • Curcumin powder:400mg, 600mg,3 times per day • Tincture (1:2) :15-30 drops ,4 times per day.

CURCUMIN IN POTENTIALLY MALIGNANT DISORDERS

Curcumin has been found to inhibit many disease processes through their anti-inflammatory, antioxidant and anticancer properties. [35]Curcuminoids isolated from turmeric, has been found to have effective antioxidant, DNA-protectant and antimutagen action.

A study concluded that usage of turmeric oil daily for 3 months had a beneficial role in treatment of OSMF. [36]

In a study it was observed that 58 OSMF patients were given turmeric in any form, i.e., alcoholic extracts of turmeric, turmeric oil and turmeric oleoresin were all effective in decreasing the number of micronucleated cells (which are found to be increased in exfoliated oral mucosal cells and circulating lymphocytes of precancerous oral lesions) both in exfoliated oral mucosal cells and in circulating lymphocytes. [37]

Deepa Das et al[38]found that turmeric dispensed in the form of cucurmin and turmeric oil was effective in the treatment of OSMF which was evident by the positive changes observed in the histopathological examination after treatment along with the significant improvement in clinical signs and symptoms.

Bhide and Jakhi reported symptomatic relief and clinical improvement in the opening of jaw with turmeric extract and turmeric oil in 30 cases of OSMF in a pilot study . The interincisural opening increased in 16/21 cases treated with turmeric oil and in 8/10 cases treated with turmeric extract. The group also reported the protective effects of turmeric on micronuclei production in peripheral lymphocyte cultures and in buccal mucosal smears from human subjects with OSMF. They further confirmed the reversal of cytogenetic damage by turmeric oil and Turmeric oleoresin (TOR) as indicated by a reduction in the number of micronuclei in exfoliated buccal mucosal smears from patients of OSMF from a mean of 10.2 + 0.28 a (mean + SD) to a 3.9 + 0.23 a (mean + SD). A therapeutic response to the symptoms of burning sensation or difficulty in opening the jaw was also reported.[4]

A study was done where oral sub mucous fibrosis was induced in mice using marketed Gutkha preparation and formulating into a mucoadhesive gel form and applying to mice oral mucosa with the help of cotton bud for a period of 6 months. In second phase, treatment was carried out following the above method using curcumin formulation. The tissue samples collected for 1, 3 & 6 months induction period & 1, 3 & 6 months of treatment period on 6 months oral sub mucous fibrosis induced mice. Histopathological observations reported that there was considerable induction of oral sub mucous fibrosis and excellent treatment results on curcumin usage. The results of the present study of mucoadhesive semi-solid drug design for the

treatment of oral sub mucous fibrosis will be useful for drug industry for the benefit of patients suffering from oral sub mucous fibrosis. [39]

A study was done to evaluate the efficacy of curcuminoids in controlling the signs and symptoms of oral lichen planus, at doses of 6000 mg/d (3 divided doses), and their safety at this dose. Results showed high-dose curcuminoids are efficacious in the reduction in symptoms and signs of oral lichen planus.[40]

In a prospective trial of patients at high risk for the development of epithelial cancer in several organs, oral intake of curcumin up to 8 g/day had no toxic effects in humans and led to histologic improvement of oral leukoplakia in 2 of 7 patients during 3 months of administration .[32]

In 25 patients with oral leukoplakia treated with 900 mg curcumin, 80 mg desmethoxy curcumin and 20mg bisdesmethoxy curcumin per day, serum and salivary vitamin C and E levels were found to increase, while markers for oxidative stress in serum and saliva decreased. [41]

CONCLUSION

Curcumin possesses wide-ranging anti-inflammatory and anti-cancer properties. Many of these activities can be attributed to its potent antioxidant capacity at neutral and acidic pH, its inhibition of cell signalling pathways at multiple levels, its diverse effects on cellular enzymes and its effects on angiogenesis and cell adhesion. In particular, curcumins ability to affect gene transcription and induce apoptosis in preclinical models advocates its potential utility in cancer chemoprevention and chemotherapy.

The pharmacological safety and efficacy of curcumin makes it a potential compound for treatment and prevention of a wide variety of human diseaseses.From earlier experimental and clinical data and the results of extended clinical Phase I trial of turmeric oil concluded that curcumin has potential chemoprotective agent in patients of oral submucous fibrosis, which is otherwise irreversible and potentially precancerous.

Its diverse molecular targeting capability makes it an appropriate agent for the prevention & therapy of numerous human pathological conditions,particularly in oral submucous fibrosis. Thus, a trip back to our “roots” to explore the “roots” of Curcuma longa as a source for better treatments will certainly prove productive. As Hippocrates said almost 25 centuries ago, “let food be thy medicine and medicine be thy food.” curcumin may indeed be the medicine & food that the world has long been looking for ,in every area of human health.

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