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Abstract:

Curcumin is a component of turmeric and used in Ayurvedic medicine. It has wide range of properties such as anti inflammatory, anti oxidant, anti fungal, hepatoprotective, anti platelet, anti microbial, anti cancerous properties. It also has a treatment effect in various oral lesions such as leukoplakia, lichen planus, oral ulcers, etc., It has poor bio availability ,so higher plasma concentration cannot be obtained. It has both beneficial and adverse effects. This article is a review of the properties and effect of curcumin in oral lesions and its adverse effects.

Key words*: Curcumin, properties, oral lesions, adverse effects.*

Introduction

Curcumin is the active ingredient in the dietary spice,Turmeric[1],which belong to the family Zingiberaceae[2]. It is known to be one of the oldest spices that have been used in western and southern parts of India and in a major part of Ayurvedic medicine[2]. The medicinal history of curcumin is approximately 2500 years old [3] .

Chemistry and structure of curcumin

Curcuminoids are components of turmeric which include curcumin, demethoxycurcumin, bisdemethoxycurcumin and cyclic curcumin[4]. Milobedzkaand Lampe identified the chemical nature of curcumin as diferuloyl-meltrane or 1,1-heptadiene, 3,5-dione-1,7 bis(4 hydroxy-3 methoxy phenyl)[5]. It is a liphophilic polyphenol that is insoluble in water but is quite stable in the acidic pH of stomach[3].

Composition of turmeric

Curcuminoids (1-6%); volatile oils(3-7%); fibers(2-7%); mineral matter(3-7%); protein(6-8%); fat(5-10%); moisture(6-13%); carbohydrate(60-70%)[6].

Properties of curcumin

Anti inflammatory properties

The anti inflammatory action of curcumin is due to its ability to

- Inhibit biosynthesis of prostaglandins from the Arachidonic acid pathway.
- Inhibits neutrophil function[7].
- Inhibits LOX (lipoxygenase) and COX(cycloxygenase) activities, suppresses

the nuclear factor kappa-β(NFK-β) activation.

- It inhibits production of proinflamatory monocyte/macrophage derived cytokines IL-1,-2,-6,-12, MCP-1, IL-1β, TNF-α in peripheral blood monocyte and alveolar macrophages[1,3].
- Lowers histamine levels and increases the production of natural cortisone by the adrenal glands[7].

Anti oxidant properties

The strong anti oxidative property is mediated

- Through enzymes such and superoxide, dismutase, catalases, glutathione peroxidase.
- By scavenging the reactive oxygen species(ROS).
- By inhibiting the oxidative DNA damage.
- By interacting with oxidative cascade and prevents its effect.
- By enhancing the synthesis of intracellular antioxidant, glutathione[3].
- By increasing cellular resistance to oxidative[7].

Anti platelet properties

Curcumin inhibits the formation of thromboxane A2 (TXA2) by platelets and prevents their clumping action[7]. It also inhibits the platelet aggregation mediated by epinephrine, platelet aggregation factor(PAF), collagen, adenosine diphosphate(ADP)[8].

Antimicrobial properties

Curcumin inhibits the growth of many bacteria, virus, fungal, and parasites. It demonstrates antibacterial effect against 13 bacteria and anti candidial effect was demonstrated against 38 different stain of candida. It is proved to be effective compound to inhibit HIV-1 LTK directed gene expression without any major effect on cell viability[9].

Hepatoprotective properties

This effect of curcumin is due to its antioxidant effect. The ability of curcumin to inhibit several factors like nuclear factor-kb, which modulates the pro inflammatory and profirotic cytokines as well as its antioxidant effect, which is the molecular basis to use in hepatic disorders. It attenuates liver injury induced by ethanol, thioacetamide, iron over dose, cholestasis, CCL_4 intoxication, galactosamine, acetaminophen[7,10].

Anti cancer properties

Curcumin inhibits cell-cycle progression, both of which prevents cancerous cell growth. The anti proliferative effect is mediated through inhibition of protein kinase and mRNA expression and apoptotic effect may partly be mediated through inhibition of protein tyrosine kinase, protein kinase c. It inhibits carcinogenesis at three stages: tumor promotion, angiogenesis and tumor growth.This property is also due to its anti oxidant effect[7].

Mechanism of action of curcumin in oral lesion

Curcumin shows to be effective against precancerous lesions by significantly increasing the local and systemic anti oxidant status through increased vitamin C and vitamin E, decreased lipid peroxidation and DNA damage, which suggested that the anti-precancerous effect is through the anti-oxidant and pro-oxidant pathways[11,12].

Leukoplakia

Due to its anti cancer and anti inflammatory properties curcumin is useful in the treatment of oral leukoplakia[13]. A study shows that the value of serum and salivary vitamin C and vitamin E showed statistically significant decrease and increased MDA(melanodialdehyde) and 8-OH dG(8 hydroxy -2 deoxyguanosine) levels in oral leukoplakia as compared in normal levels[11,14]. There are reports which suggest that curcumin quenches ROS production and acts as anti oxidant[11].

Oral lichen planus

The anti inflammatory property and anti oxidant property of curcumin plays a role in the treatment of oral lichen planus. It is said that oral lichen planus is a chronic inflammatory disease with the immune system having the primary role in development of the disease. According to Rao CV et al, curcumin is the dual inhibitor of arachidonic acid metabolism and thus inhibiting the products of inflammation[15]. Recent studies have reported increased oxidative stress and imbalance in the anti oxidant defense system in patients with oral lichen planus. This leads to disturbed antioxidant defense, lipid peroxidation and increased oxidative modification of proteins in dermis of oral lichen planus patients. As curcumin is a stong anti oxidant, it has curative and preventive effects[16].

Oral submucous fibrosis

Myofibroblast plays an important role in this disease. Curcumin inhibits cell proliferation in fibroblast and myofibroblast. Curcumin treatment results in a dose dependent increase in the proportion of myofibroblast cells in G0/G1 phase. It induces cell apoptosis in these cells[17]. Rai B et al conducted a study in which 25 patients with OSMF treated with curcumin showed significant decrease in burning sensation and improvement in mouth opening[13].

Candidiasis

Curcumin seems to be effective against candidiasis because of its anti fungal effect. A study suggest that curcumin induced leakage of intracellular components particularly potassium ions from C andida albicans. Loss of cytoplasmic potassium would lead to cell death in fungi. Lee et al assume that curcumin forms electrostatic and/or hydrophobic interactions with fungal cell membrane and cell wall disruption[18]. Candida albicans is the most susceptible to curcumin among the candida species. It completely abolishes the growth of fungi stains and prevents the adhesion of candida species to epithelial cells[19].

Apthous ulcers

Curcumin is used in the treatment of apthous ulcer as it has the anti inflammatory property[13] and wound healing property by increasing cellular proliferation and collagen synthesis at the wound site as evidence by increasing total protein and type 3 collagen content of wound tissue leading to further rate of epithelisation, wound contraction and increases tensile strength and it also relieves pain[20].

Oral cancer

The mechanisms by which curcumin exerts its anti cancer effects are comprehensive and diverse with multiple targets.

- It suppress the transformation, proliferation and metastasis of cancer cells.
- It has anti cancer activity against oral squamous cell carcinoma by inhibiting the cell proliferation, invasion and by inhibiting the activation of EGFR (epidermal growth factor receptor) signaling and inhibits the expression of MMPs (matrix metalloproteinase) and PAs which are involved in tumor metastasis[21,22].
- Curcumin inhibits the proliferation of cells, induces apoptosis and causes accumulation of cells in G2/M phase of cell cycle.

- Curcumin down regulates the expression of NF-kβ, COX-2, TNF (tumor necrosis factor) and activates host macrophages as well as natural killer cells.
- Curcumin also affects the cell-cell adhesion proteins and inhibits the production of cytokines relevant to tumor growth[23].
- Curcumin has been shown to shown interfere with many of the process involved in angiogenesis. Early studies demonstrated that curcumin inhibits fibroblast growth factor (FGF) induced neovascularization[1].

Pharmacokinetics

Curcumin has poor bioavailability, which appears to be mainly due to poor absorption, rapid metabolism and systemic elimination[5].It is absorbed in intestine and metabolised in liver and eliminated in feaces and a little or no curcumin in urine. Higher concentrations cannot be achieved and maintained in plasma and tissues due to its extensive metabolism[24].

Preparations and trade names

Curcumin is available as capsules containing powder, fluid extract, tincture, powder, oil gel, mouthwash, oral paste, lozenges, pit and fissure sealant, sub gingival irrigant, intracanal medicament[25,26].

Trade name: Turmix capsule amd mouthwash, Novel nutrient curcumin, Biocurcumin, Bio AV curcumin, Myristin, Lacferin c soft gel, Mervia, Theracurmin,etc.

Dosage

Chanani Wu et al reported that curcuminoids at doses of 6000mg/day in three divided doses were well tolerated and could prove efficacy in controlling signs and symptoms of lichen planus[12]. Rai et al previously reported curcumin efficacy when given orally for treatment of precancerous lesions at a dose as high as 8g/day. The results showed significant symptomatic relief and also reduction in clinical size of the lesion by treatment with curcumin[12]. In the study conducted by Rai B et al with curcumin capsules(900mg curcumin) shows to be effective in the treatment of OSMF[13,26]. Manifar S et al showed that curcumin gel containing 2% curcumin is effective againt aphthous ulcer[26]. A study by Martin et al shows that curcumin at a dose of 64mg/ml inhibits the growth of Candida albicans[19]. The most effective dosage of curcumin is currently unknown, recommended dosage range from 1000-8000mg per day in 1-3 divided doses[27].

Drug interactions

Curcumin may affect the bloods ability to clot and could interfere with anti platelet and anti coagulant drugs such as warfarin, clopidogrel, aspirin and enhances their action. It also interferes with the drugs such as cimentidine, lansoprazole, omeprazole by increasing the production of stomach acid. Curcumin may increases the effect of hypoglycemic drugs and increasing the risk of hypoglycemia[25]. A study on the interactions between curcumin and NSAIDs shows that these may be synergy between them[28].

Adverse effects

Curcumin is regarded as safe by FDA. Only a few clinical studies of oral curcumin and curcuminoids have reported perceptible side effects at doses ranging from 180mg to 12g[27]. A clinical study in human with high doses (2-12g) of curcumin have shows side effects with some subjects reporting mild nausea and diarrhea. More recently, curcumin was found to alter iron metabolism by chelating iron and suppressing the protein hepcidin, potentially causing iron deficiency in susceptible patients[29]. In 1976 Good pasture and Arrighi found the turmeric caused a close and time dependent induction of chromosomal aberration in several mammalian cell lines, these alterations are observed at concentration of 10µg/ml[24]. Excessive dosages of curcuminoids could cause ulcers and reduction in RBC and WBC[25]. It has anti thrombotic activity interfering with blood clot formation[7].

Contraindications

It is contraindicated in patients with gall stones, as it has the potential to trigger biliary colic[27]. In cultured cells curcumin exhibits the properties of an iron chelator, making it likely that it could induce a subclinical or clinical iron deficiency anemia and should taken with caution among those with marginally low iron stores or other diseases associated with iron such as anemia in chronic disease[30]. In diabetic patient, curcumin may lower blood sugar levels and when combined with medications for diabetes could cause hypoglycemia[25].

Conclusion

Curcumin has large number of benefits in the treatment of many diseases and it is used as a natural medicine from the ancient times. As the concentration of curcumin cannot be obtained at a higher level in the plasma and tissues, the adverse effects caused by it's over dosages cannot be studied properly. So

further study and trials are needed to use the curcumin as a effective medicine in the treatment of oral diseases in the future.

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