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CURCUMIN IN THE MANAGEMENT OF ORAL POTENTIALLY MALIGNANT DISORDERS

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ABSTRACT

The use of herbal agents in medicine and dentistry is gaining importance worldwide. One such nutraceutical is turmeric which has come all the way from kitchen to clinic. Historically, turmeric finds a place in ancient Ayurvedic, Sidhha, Unani and Chinese systems of medicine. Although they are very popular in their day-to-day use, only few medicinal herbs have been scientifically evaluated for their potential in medical treatment. Several components, more than 100, have been isolated from turmeric. Curcumin, the principal curcuminoid, comprises of approximately 2-5% of turmeric. Curcumin is a natural polyphenolic product derived from turmeric which exhibits therapeutic activity mainly due to its chemical structure and unique physical and biological properties. Curcumin was first isolated in 1815 and its chemical structure was determined in 1973. Chemically, it is a diferuloyl methane molecule [1, 7-bis (4-hydroxy-3- methoxyphenyl)-1, 6-heptadiene-3,5-dione)] containing two ferulic acid residues joined by a methylene bridge. As a natural product, it is nontoxic and has little or no adverse effects. Safety evaluation of curcumin reveals that when curcumin was given to Wistar rats, guinea pigs and monkeys of both sexes at a dose of 300 mg/kg body weight, no pathological, behavioral abnormalities or lethality was observed. No adverse effects were observed on both growth and the level of erythrocytes, leucocytes, blood constituents such as haemoglobin, total serum protein, alkaline phosphatase, etc. Human clinical trials also indicate that curcumin has no toxicity when administered at doses of 1–8 g/day140and 10 g/day. Curcumin is not only responsible for the yellow color of turmeric but accounts for most of its pharmacological effects. It exhibits a big promise as a therapeutic agent due to its properties like antioxidant, analgesic, anti-inflammatory, antiseptic activity, anticarcinogenic activity, chemopreventive,

chemotherapeutic activity, anti-tumour, antiviral, antibacterial, and antifungal and is currently in human trials for a variety of conditions. The applications of curcumin in dentistry include its use as pit and fissure sealant, dental plaque detection system, subgingival irrigant and intracanal medicament. The antioxidant, anti-carcinogenic and anti-inflammatory properties of curcumin makes it appropriate to explore the role of curcumin in oral potentially malignant disorders (OPMD). OPMD represent a family of morphological alteration amongst which some may have an increased potential for malignant transformation. Potentially malignant disorders of the oral mucosa are also indicators of risk of likely future malignancies elsewhere in (clinically normal appearing) oral mucosa and not only sites specific predictors. In this review use of curcumin in OPMD like oral submucous fibrosis (OSMF), oral leukoplakia, oral lichen planus (OLP) and lesion associated with reverse smoking will be discussed. Various formulations of curcumin, its dosage, duration of therapy, outcomes used for reporting its efficacy and safety, adverse effects, and follow up will be analyzed for each of these conditions and presented. The mechanism of action of curcumin in OPMD will be elaborated. The intended audience/readership are the researchers working in the field of pharmacology, pharmaceutical industry and pharmacotherapy. It will equally benefit the clinicians dealing with OPMD as this chapter intends to synthesize the current data on use of curcumin in OPMD and suggest evidence-based future recommendations. Additionally, researchers in the field of oncology and cancer research are potential audience for this chapter.

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1.1 INTRODUCTION

Curcumin is the bright yellow-orange chemical produced by some plant. It is the principal curcuminoid of the most popular Indian spice turmeric (Curcuma longa), member of the ginger family (Zingiberaceae). The other two curcuminoids are desmethoxycurcumin {curcumin II} and bis-desmethoxy curcumin {curcumin III}. The curcuminoids are natural phenols and are responsible for the yellow color of the turmeric. Commercial curcumin contains curcumin I [77%], curcumin II [17%] and curcumin III [3%] as its major components. Curcumin is a diarylheptanoid belonging to the group of curcuminoid. It possesses pharmacological properties due to its inhibitory effects on metabolic enzymes. Curcumin, a natural phenolic compound has potent antitumor, anti-inflammatory, antioxidant properties. It is a potent chemopreventive agent as well as having chemotherapeutic activity. It inhibits production of inflammatory cytokines by peripheral blood monocytes and alveolar macrophages. It induces apoptosis in cancer cells and inhibits phoshol-ester induced protein kinase C activity. It easily penetrates into the cytoplasm of the cell, accumulates in the plasma membrane, endoplasmic reticulum and nuclear envelop.

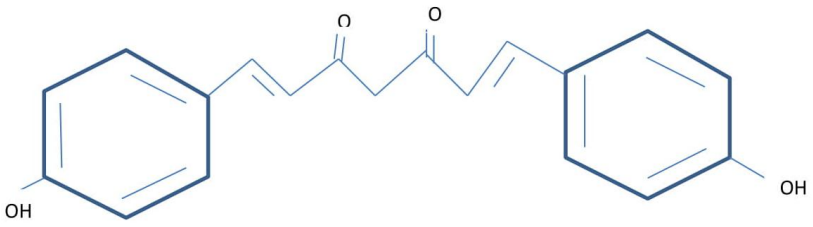
1.2 HISTORY

It is the most useful compound from turmeric. The history dates back about 5000 years. It is the main healing agent used for cuts and wounds in Indian Ayurveda Medicine. The bright orange-yellow pigment is the man source of curcumin. It is typically grown in warmer regions including India, China, and southwest Asia. After the roots are harvested, they are cleaned in water, cured and dried. After drying the roots is grounded for use as a spice. Turmeric gives curry its golden yellow color. In 1815 curcumin was first isolated, Vogel and Pierre Joseph Pelletier reported the isolation of yellow color matter from the rhizome of turmeric In1870, curcumin was obtained in crystalline form and identified as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E). After almost another hundred years its full structure was mapped in 1910 by LAMPE.[1] It probably reached China by 700 AD, East Africa by 800 AD, West Africa by 1200AD, and Jamaica in the eighteenth century.

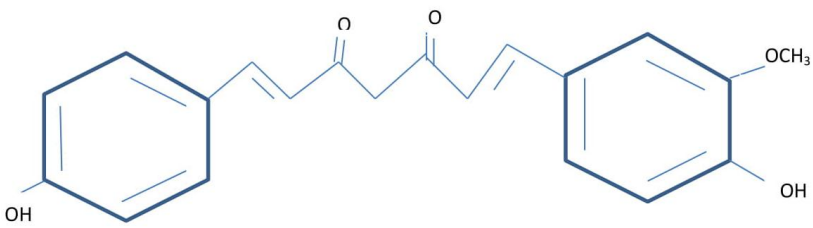
Traditionally turmeric was used for health condition like smallpox to a sprained ankle. Today we extract curcumin from turmeric to use as a natural medicine. In Ayurvedic medicine, it is used for the treatment of many inflammatory diseases, including asthma, allergies, rheumatism, sinusitis, cough, and diabetes. It is also used to treat sprain and muscle pain. In China curcumin was traditionally used to treat abdominal pain. It is used as a part of Chinese medicine around 1000years ago. Even today turmeric is used extensively in various religious and wedding ceremonies. In medieval Europe, turmeric is widely known as Indian Saffron.

India produces nearly the world's entire turmeric crop and consumes 80 % of it. Erode, a city in the south Indian state of Tamil Nadu is the world largest producer of and the most important trading center for turmeric. It is known as 'turmeric city', 'yellow city'. Sangli, a city of Maharashtra, is second only to Erode in size and importance is a production and trading site for turmeric.

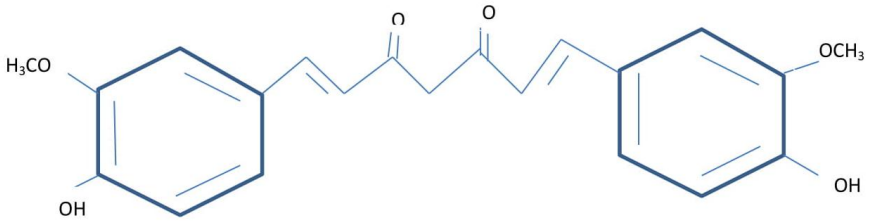
In present-day processing, rhizome is placed in shallow pans in large iron vats containing 0.05- 0.1% alkaline water [e.g solution of sodium bicarbonate]. The rhizomes are then boiled for between 40 - 45 minutes [in India] or 6 hours [in Hazare, Pakistan] depending on the variety. The rhizomes are removed from the water and dried in sun immediately to prevent overcooking.[2]



Bis-Demethoxycurcumin (CURCUMIN III)



Demethoxycurcumin (CURCUMIN II)



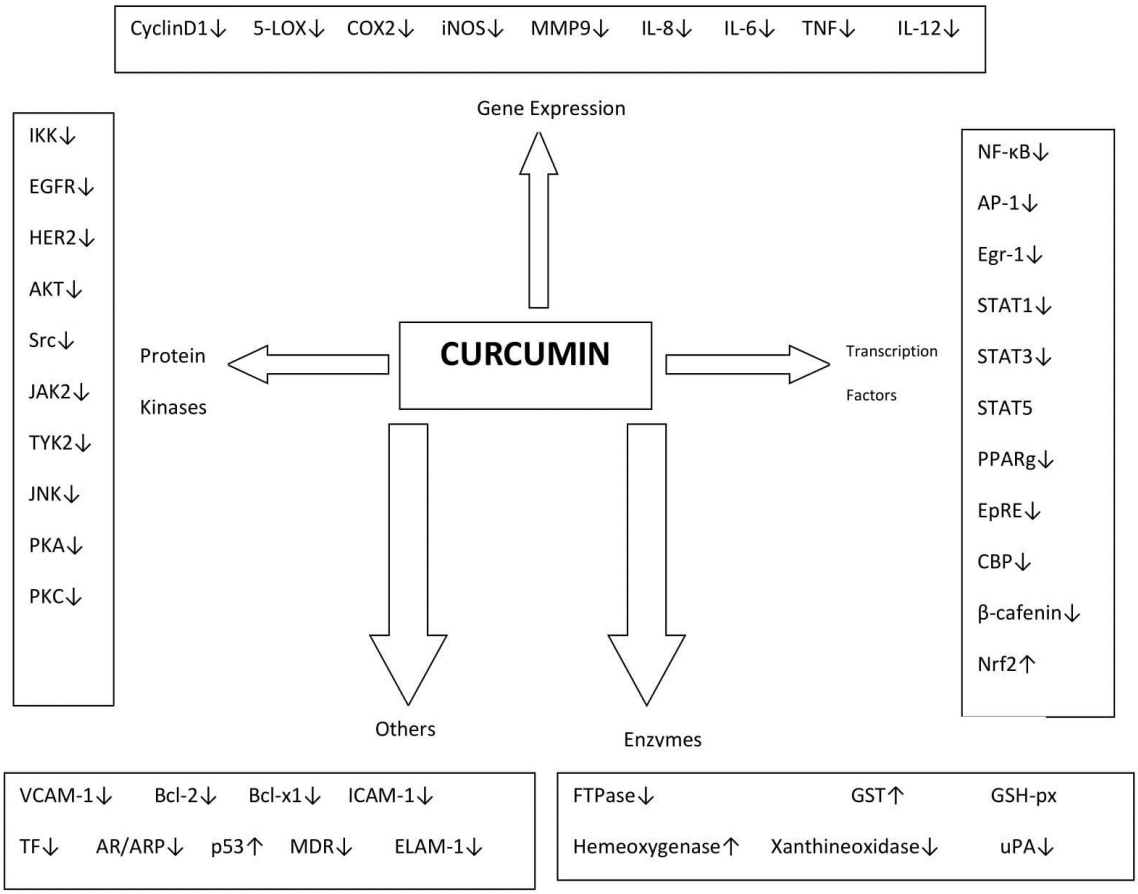
CURCUMIN (CURCUMIN I)

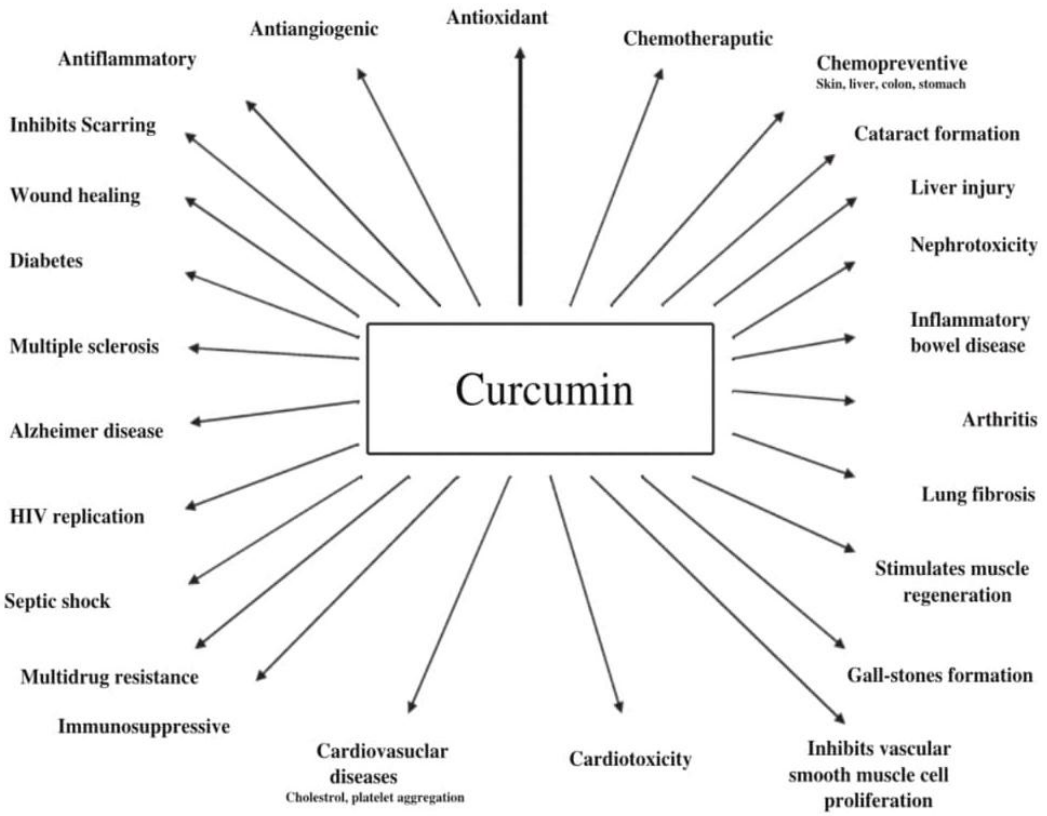
1.3 CHEMICAL STRUCTURE AND CHEMICAL PROPERTIES

Curcumin is a diaryl heptanoid belongs to the group curcuminoid which are natural phenols. It is a tautomeric compound existing in an enolic form an organic solvent an as a keto form in water. The enol form is more energetically stable in a solid phase (Figure 1 - 2D structure keto form and enol form of curcumin). Chemical name (1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Other names -Natural yellow 3, C. I. 75300. Aromatic ring system is connected by two α and β unsaturated carbonyl group. The α and β unsaturated carbonyl group is a good Michael acceptor and undergoes nucleophilic addition. It is used as a complexometric for Boron. It reacts with boric acid to form a red colored compound, rosocamine. Hence it can be used for soil boron determination called curcumin spectrophotometry. It gives brownish red color with alkali, light yellow color with acids. Curcumin molecule has two hydroxyl groups at both ends. When pH is greater than 8 electron cloud deviation occurs, curcumin turns red from yellow. Hence it is used as a pH indicator.[3] Chemical formula $C_{21}H_{20}0_6$ molecular weight 368.27, melting point 183 degrees C.

1.4 PHYSICAL PROPERTIES

Curcumin is an orange-yellow crystalline powder, lightly bitter in taste insoluble in water and ether, soluble in ethanol propylene glycol, acetic acid. Density 0.93, melting point 179-182 degree C.[4] Vapour density 13 versus air storage temperature -20 degree C. pH range = yellow (7.8) to red-brown (9.2) Curcumin shows strong reducing stability, coloring agent, sensitive to light, heat, iron ion-sensitive.[5]


CyclinD1↓ 5-LOX↓ COX2↓ iNOS↓ MMP9↓ IL-8↓ IL-6↓ TNF↓ IL-12↓
Gene Expression
IKK↓
EGFR↓
HER2↓
AKT↓
Src↓
JAK2↓
TYK2↓
JNK↓
PKA↓
PKC↓
Protein Kinases
CURCUMIN
Transcription Factors
NF-κB↓
AP-1↓
Egr-1↓
STAT1↓
STAT3↓
STAT5
PPARg↓
EpRE↓
CBP↓
β-cafenin↓
Nrf2↑
Others
Enzymes
VCAM-1↓ Bcl-2↓ Bcl-x1↓ ICAM-1↓
TF↓ AR/ARP↓ p53↑ MDR↓ ELAM-1↓
FTPase↓ GST↑ GSH-px
Hemeoxygenase↑ Xanthineoxidase↓ uPA↓


Antiangiogenic
Antioxidant
Chemotheraputic
Antiflammatory
Chemopreventive
Skin, liver, colon, stomach
Inhibits Scarring
Cataract formation
Wound healing
Liver injury
Diabetes
Nephrotoxicity
Multiple sclerosis
Inflammatory bowel disease
Curcumin
Alzheimer disease
Arthritis
HIV replication
Lung fibrosis
Septic shock
Stimulates muscle regeneration
Multidrug resistance
Gall-stones formation
Immunosuppressive
Cardiovasuclar diseases
Cholestrol, platelet aggregation
Cardiotoxicity
Inhibits vascular smooth muscle cell proliferation

1.5 BIOLOGICAL PROPERTIES

The physiochemical and structural features are associated with the biological activities of curcumin. Curcumin function as an antioxidant, anti-inflammatory, and anti-atherosclerotic. It inhibits scarring, cataract, gallstone formation, liver injury, and kidney toxicity. It provides wound healing, treatment of skin ailments, cure liver problem and digestive disorder.

1.5.1 Curcumin inhibits angiogenesis[6]

It's also an anti-angiogenic factor. It suppresses the human vascular endothelial cells and abrogates fibroblast growth factor-2-angiogenic response, thus suggesting that curcumin is also an antiangiogenic factor. CD13/ aminopeptidase N9APN0 is a membrane-bound, zinc dependent metalloproteinase that play a key role in tumor invasion and angiogenesis. It was observed that curcumin binds APN and irreversibly its activity.

1.5.2 Antiplatelet activity

Curcumin inhibits production of Thromboxane (Tx) by platelet and increases fibrinolysis. It inhibits platelet aggregation induced by ADT, collagen, norepinephrine. In comparison was significantly more potent platelet inhibitor than aspirin.

1.5.3 Antioxidant Activity

Curcumin antioxidant activity is by virtue of its chemical structure. The curcuminoid consists of two methoxylated phenols connected by α and β unsaturated carbonyl group that exist in a stable enol form. The phenolic and methoxy group on the phenyl ring and 1,3-diketone system is an important structure that contribute to its antioxidant effect. The antioxidant activity increases when the phenolic group with the methoxy group is at the ortho position. Curcumin is 10 times more active as an antioxidant than vitamin E. Compared with other antioxidants, curcumin has various types of functional groups in its structure as it exhibits beta diketogroup, carbon to carbon double bond, and phenyl rings. The anti-oxidant property of Curcumin is mainly due to the presence of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase. Curcumin inhibits lipid peroxidation (LPO). LPO has an important role in inflammation, heart disease, and cancer. It provides protection to hemoglobin from oxidation at a concentration as low as 0.8 mM.[7] Curcumin treatment also reduces NO generation and protection of neural cells from oxidative stress. Thus curcumin is useful in reducing the neuroinflammation associated with a degenerative condition such as Alzheimer's disease.[8]

1.5.4 Anti-inflammatory activity

The presence of kept form and double bonds in the structure of curcumin are mainly responsible for its anti-inflammation action.[9] Curcumin suppresses the activation of NF-kB, an inducible transcription factor that regulates the expression of a host of genes involved in inflammation, cellular proliferation, and cell survival.[10] Curcumin inhibits other pathway involved in inflammation example arachidonic acid pathway, prostaglandin E 2 synthesis through direct inhibition of microsomal prostaglandin synthesis 1.[11] Curcumin also inhibits the formation of inflammatory interleukin molecule such as IL-1, IL-2,-6,-8,-12 and chemokine. Anti-inflammatory properties of curcumin have been investigated in a number of diseases such as Alzheimer's disease, cardiovascular disease, diabetes, asthma, inflammatory diseases, arthritis, pancreatitis or renal diseases.

1.5.5 Anticancer activity

The compound is believed to interfere in all stages of cancer development, proliferation, invasion of cancer cell and also during the process of metastasis. It is regarded to be especially useful to treat cancer of prostate, colon, skin, and stomach, breast cancer by suppressing colonic aberrant crypt foci and DNA adduct formation. Curcumin is used effectively with other chemotherapy drugs to combat the cancer cells and reduces the toxic effect. It also hinders tumor formation and diffusion further in various tissues of the body. Thus along with chemotherapy, it helps to treat cancer patient better. Curcumin possesses anticancer activity via its effect on a variety of biological pathway involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumor genesis, and metastasis.[12] The important factor in chemoresistant is NF-kB. Curcumin downregulates NF-kB and inhibit I-kB kinase, suppressing cell proliferation and inducing apoptosis. Curcumin augments the cytotoxic effects of chemotherapeutic drugs including doxorubicin, cisplatin, vincristine, and melphalan. Curcumin exhibits activity against different types of cancer such as leukemia, lymphoma, gastrointestinal cancer, genitourinary cancer, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancer, and sarcoma. Anticancer effects of Curcumin are mediated through the pro-oxidant and oxidant pathways. Curcumin activates mitochondrial enzymes that lead to the production of ROS. Curcumin interacts with thioredoxin reductase, changing its activity to NADPH oxidase, which leads to the production of ROS.[13,14]

1.5.6 Chemoprevention

Curcumin inhibits carcinogenesis in all three stages- initiation, promotion, progression. It modulates transcription factors controlling Phase 1 and 2 of carcinogenesis, downregulates pro-inflammatory cytokines, free radical transcription factors, arachidonic acid metabolism via cyclooxygenase and lipoxygenase pathway and scavenges free radicals.[15,16] In the promotion stage and progression stage of carcinogenesis - curcumin decreases frequency and size of a tumor and induces apoptosis via suppression of NF-kB and AP-1 in the severe cancer type.

1.5.7 Radiosensitizing effects of curcumin

Radiotherapy plays an important role in the management of cancer. Chendil et al (2004) investigated the radiosensitizing effects in patients. Curcumin at 2 and 4 µ mol concentration in p53 mutant prostate cancer patient showed improvement to radiation-induced apoptosis. In pc-3 cells radiation upregulated TNF-α protein leading to increases in NF-kb activity and induction of BCL-protein. Curcumin in combination with radiation showed inhibition of TNF-α mediated NF-kb activity resulting in BCL-2 protein down-regulation. Thus curcumin is a potent radiosensitizer.[17] Khafif et al (2005) investigated that curcumin sensitises squamous cells carcinoma to the ionizing effect of radiation.[18] Curcumin protects from radiation-induced toxicity.[19]

1.5.8 Antibacterial activity

Curcumin suppresses the growth of several bacteria like staphylococci, streptococcus, lactobacillus.[20] Curcumin has an inhibitory effect on NF-kb activation and on the release of Interleukin-8 and cell scattering which lead to a reduction in inflammation of gastric tissue as the main cause of H. pylori infection.[21] Curcumin demonstrates a synergistic effect in combination with some antibiotics like ampicillin, oxacillin, norfloxacin against MRSA Methicillin-resistant Staphylococcus aureus strain.[22] There is an evidence of antagonistic activity against S. typhi and S. typhimurium in combination with ciprofloxacin.[23]

1.5.9 Antiviral

Curcumin as a plant derivative has a wide range of antiviral activity against different viruses. Inosine monophosphate dehydrogenase (IMP Dh) enzyme due to rate limiting activity in the denovo synthesis of guanine nucleotide is suggested as a therapeutic target for an antiviral and anticancer compound. Curcumin through inhibitory activity against IMP Dh effect in either noncompetitive or competitive manner is suggested as a potent antiviral compound via

this process.[24] Curcumin is active against a variety of viruses including para-influenza virus. Type 3 (PIV-3), feline infections, peritonitis virus (FIPV), vesicular stomatitis virus (VSV), Herpes simplex virus (HSV), Flock house virus (FHV), respiratory syncytial virus (RSV) assessed by MTT test.[25] The antiviral activity may be mediated by curcumin's ability to decrease reactive oxygen species, restore cell membrane integrity and inhibit apoptosis of the neuronal cells. The direct inhibition of HCV viral replication by curcumin is also demonstrated. Curcumin may, therefore, be useful in the treatment of patients with highly prevalent viral hepatitis, cirrhosis, and liver cancer.[26] In the study by Mazumder et al curcumin inhibited HIV replication, the mechanism for this lies in specific interaction of curcumin with the viral protein integrase and protease.[27] Overall, the finding from other research group suggested that curcumin exerts antiviral activity through a different mechanism in different viruses.

1.5.10 Antifungal

A Bazilian research team investigated the effects of curcumin against 13 strains of fungi found that curcumin was able to completely inhibit the growth of C. albicans, as well as a number of other fungal strains. Curcumin is able to stop candida from adhering to human cells. The adhesion of micro-organism to host mucosal surface is a prerequisite for colonization and infection.[28] The adhesion of Candida tropicalis to Basal epithelial cells was inhibited by 55% in the presence of curcumin while the inhibition caused by fluconazole is only 13%. Curcumin was 2.5 fold more potent than fluconazole at inhibiting the adhesion of C. albicans to BEC.[29]

1.5.11 Curcumin as a healing agent

Wounds treated by curcumin heals much faster due to an improved rate of epithelisation, wound contraction, and increased tensile strength. This is due to decreased level of lipid peroxides, levels of superoxide dismutase, catalase, glutathione peroxidase are increased.

1.6 BIOAVAILABILITY OF CURCUMIN (NANOPARTICLES)

Curcumin (1,7 bis- (4 hydroxy - 3 methoxyphenyl) - hepta - 1,6 diene -3,5 dione) is a bioactive component isolated from the rhizome of Curcuma longa. It exhibits various pharmacological activities. But the pharmaceutical application of curcumin was limited due to its poor water solubility and bioavailability. The therapeutic efficacy of curcumin nanoparticles increases by applying the drug in different nanoforms. Curcumin nanoparticles

possess remarkable antibacterial, antiviral, antiprotozoal activity. Hence curcumin nanoparticle loaded nanogel, microemulsion, nanocream can be used for drug delivery.

The Nanoparticle have been used extensively in medicine like drug delivery, probing of DNA structure

- Detection of protein
- Tissue engineering
- Detection of pathogen
- Destruction of cancer cells
- Phagokinetic studies[30]

The advantage of using nanoparticles-

- large surface area
- controlled particle size
- site-specific targetting
- bio-availability
- stability
- bio-degradable and controlled release of drugs[31]

The therapeutic use of curcumin was confined due to its poor water solubility, instability, and low bioavailability.

The reasons for low bioavailability of curcumin are:

- poor absorption
- high metabolic rate
- rapid systemic clearance[32]

Methods of synthesis of curcumin Nanoparticles.

- Wet milling method
- Micronuclei on
- Solvent Evaporation method
- Single emulsion method
- Spray drying method
- Nanoprecipitation method
- Coacervation technique
- Anti-solvent precipitation method

- Ultrasonicstoon
- Ionic gelation method
- Feeding method
- Emulsion polymerization method
- Solid dispersion method
- Thin film hydration method

Nanocurcumin prepared by a process of wet milling technique was found to have a narrow particle size distribution in a range of 2 - 40 nm. Curcumin showed to be more freely dispersible in water leading to more antimicrobial activity.[33] Curcumin nanoparticles show higher anti-oxidant property than Curcumin due to a decrease in the size of Curcumin and the formation of an amorphous state.[34] Curcumin nanoparticles and microemulsion are also known for its anti-microbial activity. Formulated Curcumin microemulsion such as Curcumin -loaded myristic acid microemulsion is used to inhibit Staphylococcus epidermidis, which is mainly responsible for nosocomial infections.[35] Villa and coworkers reported that the anti-microbial activity of Curcumin can be improved by the formation of Curcumin– encapsulated chitosenpolyvinyl alcohol silver nanocomposite film.[36] From the cellular uptake and microscopy study, it was noticed that Curcumin modified nanoparticles are more potent compared to free Curcumin.[37] Curcumin nanoparticles cause inhibition of NF – kB and suppression of NF-kB – regulated protein involved invasion. (MAP-9), angiogenesis (VEGF).[38] Curcumin possess anti-cancerous properties due to its inhibition of various signaling pathways. It was found that the aqueous dispersion of nanocurcumin was much more effective than curcumin against S.aureus, B.Subtilis, E.coli, P. aeruginosa, P. notatum, and Aspergillus Niger. The activity of nanocurcumin was more pronounced against Gram + bacteria than Gram - bacteria. Its antibacterial properties are much better than antifungal activity. Nanocarriers like curcumin-loaded PLGA (Polylactide -co - glycoside) and curcumin nanoparticle formulation have better bio-activity and bio-availability as well as increased cellular uptake compared to curcumin were reported. Native curcumin and PGLA – curcumin inhibited the increase in the serum level of inflammatory cytokinesis and chemokine. The increase in IFN Ɣ was inhibited by 25% with native curcumin and 75% with PGLA – curcumin. Oral PGLA was effective as curcumin at a 15 fold lower concentration. PGLA -curcumin was superior in inhibiting the sequestration of parasitized RBC and CD8 + T cell in the brain. P GLA -curcumin has better bioavailability and has a potential to be used

as an adjuncts drug to use in human cerebral malaria.[39] Curcumin nanoparticles increase the chemotherapeutic effect of anticancer drugs.[40]

1.7 CURCUMIN IN ORAL LICHEN PLANUS

Oral lichen planus is an immunological mucocutaneous disease with a wide range of clinical appearances. The treatment of oral lichen planus is difficult and disappointing. The oral form exists more frequently than the cutaneous form and tends to be more resistant.

It is present frequently in the fourth decade of life with women predilection.[41,42]

OLP present as white striations, white papules, white plaque, erythema or blisters.

The buccal mucosa, tongue, gingiva are the most involved areas of the mouth.[43]

OLP clinically presents as mild painless white keratotic lesions to painful erosions and ulcerations. The reticular form present as papules and plaques with white interlacing keratotic lines (Wickham striae).

Types of lichen planus:

- Reticular
- Papular
- Plaque-like
- Erosive
- Atrophic
- Bullous

The Pathogenesis

The exact pathogenesis of OLP is not well known. It is believed to result from antigen-specific mechanism which causes dysregulation of T-cell mediated response. Dysregulation of T - cell-mediated immunity leads to the attack of activated CD8+ lymphocyte on basal keratinocyte. Non-specific mechanism includes mast cell degranulation and matrix metalloproteinase (MMP) activation mediated response. OLP chronicity may be due to deficient antigen-specific TGF-BETA 1 mediated immunosuppression. Involvement of TNF - A, CD 40, Fas, MMPs, and mast cell degranulation in disease pathogenesis. A major role in the pathogenesis of long-lasting inflammatory process is by activation of nuclear factor kappa B, a primary transcription factor which upon translocation to the nucleus, binds to a promoter region of different gene encoding immune and pro-inflammatory mediators.[44] Patients affected by oral lichen planus are often subjected to medical treatment for long periods. The drug of choice is immunosuppressive drugs. Immunosuppressive agents affect the severity

and progression of oral lichen planus but also triggers malignant transformations. Mucosal atrophy, secondary Candidiasis, systemic toxicity. To avoid systemic toxicity, herbal medicine can be used. Alternate treatment includes retinoids, ultraviolet phototherapy, steroid-sparing agents (hydroxychloroquine, azathioprine, mycophenolate mofetil) and pimecrolimus.[45] Curcumin is found to be as useful in treating cases with recurrence. Curcumin reduces pain, erythema, and ulceration.[46] Curcumin shows immunomodulatory effects involving activation of host macrophages and natural killer cells. It also provides modulation of lymphocyte-mediated function. Curcumin is shown to decrease the size of lesions and provide symptomatic relief. Curcumin increased the levels of vitamin C and E, while it decreases lipid peroxidation and DNA damage in precancerous lesions.[47] In 2010 Rai et al noted the levels of serum in saliva glands, malondialdehyde [MDA], 8- hydroxy -2-deoxyguanosine [8- OHd], the levels of vitamin C and E in patients receiving curcumin. The levels of vitamins, markers in saliva, increased while levels of MDA and 8 - OHd levels decreased.[48] According to study, higher doses (up to 6000mg/day) of curcumin in 3 divided doses provide relief in oral lichen planus patients. Whereas smaller dose (< 200mg/day) have failed to provide relief.[49] In 2012, studies conducted by Vibha Singh et al showed the improvement in the symptom after applying an extract of turmeric as an ointment for a period of 3 months.[50] The curcumin is found to be an effective alternative treatment in oral lichen planus. The chances of reoccurrence were also reduced. Curcumin has an advantage over corticosteroid as steroid can cause mucosal atrophy and candidiasis.

1.8 ROLE OF CURCUMIN IN LEUKOPLAKIA

Leukoplakia refers to a firmly attached white patch on a mucous membrane which is associated with an increased risk of cancer.[51,52] It is a precancerous lesion, a tissue alteration in which cancer is more likely to develop.

Risk factors for formation inside mouth include:

- Smoking
- Chewing Tobacco
- Excessive Alcohol
- Use of betel nuts[53]

Leukoplakia is considered as the most common premalignant lesion. The estimated prevalence rate of leukoplakia is 2% worldwide. These lesions are present particularly in the floor of mouth, tongue, lip, and Vermilion have a high risk of malignant potential.

LEUKOPLAKIA	RISK OF MALIGNANCY %
Early	Not assigned
Homogenous	1 - 7 %
Verruciform	4- 15 %
Speckled	8 - 47 %

Management of leukoplakia includes the elimination of risk factor like tobacco abuse, betel chewing, alcohol abuse, candida infections. Conservative treatment includes the use of vitamin (A, C, E), fenretinidine, carotenoids, bleomycin, a protease inhibitor, anti-inflammatory, green tea, curcuma. Surgical treatment includes conventional surgery, electrocoagulation, cryosurgery, laser surgery. Most cancer can be prevented if diagnosed at an early stage. The correct diagnosis and right treatment at the right time of potentially malignant disorder may prevent malignant transformation of these lesions. The main purpose of management is to avoid malignant transformation of the lesion. In a study conducted by Balwant Rai et al, the value of serum and salivary vitamin C and E showed significantly decreased value in oral leukoplakia as compared to normal health. The levels while significantly increased in all groups after giving curcumin. The Malonaldehyde (MDA) and 80HdG levels were increased in oral leukoplakia patients, while the levels decreased in all groups after giving curcumin.[54] It may be due to curcumin-induced production of vitamin C and vitamin E. Curcumin prevent DNA damage by decreasing the oxidative stress. On the basis of safety and toxicity profile, in severe clinical trials, the targeted dose for curcumin is between 4000mg – 8000 mg to obtain a maximum therapeutic effect.[55] In another study, the reduced size of the lesion was noted in 10 patients out of 62 receiving turmeric.[56] Combined effect of Metformin Hydrochloride along with curcumin is founded to help prevent oral cancer from forming in patients with an oral malignant lesion.

1.9 ROLE OF CURCUMIN IN ORAL SUBMUCOUS FIBROSIS

OSMF is a potentially malignant condition with characteristic features of stiffness of mucosa & restricted mouth opening. Pindborg defined OSMF as “insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx, occasionally preceded by vesicle formation, always associated with juxtaepithelial inflammatory reaction followed by a fibroelastic change of lamniapropia with epithelial atrophy leading to stiffness of oral mucosa, trismus and inability to eat.[57] This precancerous condition is caused by areca nut chewing. The fibrosis of oral mucosa and deeper tissues leads to stiffness and limitation in

the opening of mouth and protrusion of the tongue. It also causes difficulty in eating, swallowing and phonation.[58] Agarwal N et al conducted a study to find the result of using turmeric in 30 OSMF patients. Curcumin exerted anti-inflammatory activity by inhibiting the process of inflammation. It also shows fibrinolytic property due to inhibit lipid peroxidation and also check cellular proliferation. Thereby reducing cellular proliferation.[59]

Patients with OSF have two characteristic complaints include:

• Inability to open their mouth and function normally.

• Burning sensation and intolerance to spicy food.

Treatment

The total dosage of topical corticosteroids should not exceed 50g/week because of its ability to suppress hypothalamic-pituitary-adrenal axis. Curcumin has no toxicity when administered at a dose of 10g/day. None of the patient administered with curcumin reported any GIT disorder, rashes or allergy. Curcumin offers anti-inflammatory effect through inhibition of NF-kβ. Yadav M et al conducted a study of comparison of curcumin with Intralesional steroid injection. There occurs an improvement in burning sensation, inter-incisional distance, and tongue protrusion.[60] Rao et al have shown the scavenging effect of curcumin on superoxide radical, hydroxyl radical and lipid peroxidation. Due to which there is a reduction in burning sensation with normal and spicy food.[61] One of the most recent publications is a randomized control trial by Pipalia. This study evaluated the effectiveness of turmeric with black pepper & Nigella sativa in OSMF patients with improved mouth opening, burning sensation and increased superoxide dismutase level in OSMF. Black pepper prevents the metabolism of curcumin and increases its bio-availability. Nigella sativa was used due to its antioxidant, anti-inflammatory, anti-carcinogenic and antifibrotic properties.[62] Balwant Rai conducted a study of curcumin in premalignant lesions based on serum and salivary markers of oxidative stress. Curcumin increase level of Vitamin C & prevent lipid peroxidation and DNA damage. This suggests that curcumin exert its anti-cancerous effect by the pro-oxidant & antioxidant pathway.[63] In the study by Zhang SS, an antifibrinolytic effect of curcumin in TGF-β1 induced myofibroblast from human oral mucosa was studied. It was found that curcumin inhibits fibroblast & myofibroblast. It also disturbs the cell cycle, induces apoptosis by downloading BCI-2, Bax ratio and decreases generation of collagen Type 1 and Type III in myofibroblasts.[64] Another study conducted by Deepa DA et al showed anti-inflammatory action and fibrinolytic properties.[65] Various studies conducted on

the efficacy of curcumin in treating OSMF has shown marked improvement in symptoms in patients. So curcumin use of curcumin should be frequent and should be prescribed by clinicians.

1.10 ROLE OF CURCUMIN IN LESIONS DUE TO REVERSE SMOKING

Reverse smoking is smoking with the lightened end inside the mouth.[66] Reverse chutla (crude form of cigar) smoking is mainly practiced among females of Srikakulum district of Andhra Pradesh. According to Gavarasana and Susaria, the frequency was 6.23 times higher in females than males.[67] The annual age-adjusted incidence rate of palatal changes was 24.9 per 1000 men & 39.6 per 1000 woman, peak incidence was observed in 55-64 years of age. The clinical manifestations with reverse smoking are different from conventional smokers. The commonly affected areas are palate and tongue.[68] The clinical features include keratosis, hyperpigmentation, patches, red areas, ulcerated area, potentially malignant lesions, and area of palatal mucosa devoid of pigmentation.[69] The regression rate is higher when the habit was discontinued malignant transformation was 0.3% of the palatal lesion. This is a peculiar habit of the fishermen of rural Andhra Pradesh, India. This practice of smoking in the local language is called "Adda Poga". The smoking device is homemade cigar made by crudely rolling semi-dried tobacco twigs called chutta. The characteristic feature of this habit is that lighted end is kept inside the mouth and the mouth is closed, thus allowing slow inhalation of smoke from chutta. This raises a temperature of the mucosal surface with 120 degree Celsius, according to Qugley et al, this is the main reason for malignant transformation of the lesion. There is also higher content of nicotine, total particulate matter and incomplete combustion of chutta tobacco.[70] The habit thus produces a high frequency of palatal cancer,[71,72] Palatal changes occur in about 46% of reverse smokers.[73] The usual treatment was palliative quitting the habit & using antioxidant medication. In the study conducted changes and improvement in the clinical appearance of a palatal lesion and histopathological smears (moderate dysplasia turning to milder dysplasia) was observed on using curcumin with no associated allergy and untoward effects. Curcumin can be tolerated to a dose as high as 2g/day without any side effect in the latest report by Siwak DR et al and Law CD et al.[74,75] Turmeric-suppresses tumor promoter-induced activation of transcription factor NF-Kβ and AP-1.[76] It also exerts anti-precancerous effects of Vitamin C and E and prevent lipid peroxidation and DNA damage. Turmeric induces tumor cell death through the generation of reactive oxygen intermediates which was inhibited by N-acetyl cysteine.[77] In one study conducted, an acrylic palatal plate was fabricated to dispense the medication (curcumin oral

gel) so that it remains with the tissue for a longer period and is not washed away by saliva. The medication was applied for 3-4 times daily and placed in the mouth for 3-4 hours. There was half reduction in clinical severity in patients.[78] Thus, curcumin is effective in reducing the severity of the lesions.

Conflict of interest-nil.

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