

## **CURCUMIN- A MAGICAL MEDICINE: A COMPREHENSIVE REVIEW**

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### **ABSTRACT**

Since ancient time plants have been a major source of medicine. Curcumin (diferuloylmethane) is an orange-yellow component of turmeric (*Curcuma longa* Linn), a spice which is often found in curry powder. *Curcuma longa* Linn (Turmeric) has a long history of use as dye, flavouring agent and medicinal herb which is widely used in Asian countries. The yellow color of turmeric is because of curcumin, which was first isolated almost two centuries ago, and its structure as diferuloylmethane was determined in 1910. It is the most active polyphenolic constituent of turmeric which is responsible for its antioxidant, anti-inflammatory, immune-modulator and anti-tumorigenic nature. These effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. This review article is to highlight the pharmacological action and efficacy of curcumin in oral health maintenance.

**Keywords:** Curcumin, Pre-cancerous, Oral health, Anti-oxidant, Anti-inflammatory.

### **INTRODUCTION**

*Haridra* (*Curcuma longa* Linn.) of the family Zingiberaceae has esteemed medicinal properties referred in Ayurveda and has been widely used in India since ancient times in Ayurveda. Perhaps the oldest of these involves the use of natural products like *haridra*. Natural products such as curcumin *longa* Linn, which is obtained from plants have proved to be a rich source of potential anti-cancer therapies. Curcumin, a compound which is most commonly

used in the human food supply, represents a near perfect starting point for having the potential of anti-cancer therapy.<sup>1</sup> Turmeric, otherwise known as *Curcuma longa*, is a member of the ginger family, Zingiberaceae. The Latin name is derived from the Persian word, kirkum, which means saffron, in reference to the rhizomes vibrant yellow-orange color. It is indigenous to southeast Asia, but has long been used and cultivated throughout India.<sup>2</sup> Turmeric

(*Curcuma longa*) is an ancient dye, flavouring and medical herb, widely used in Asian countries. It is a herb that has been widely used in Indian medicine, cookery, and cosmetics. Curcumin has a surprisingly wide range of beneficial properties includes anti-inflammatory, antioxidant, chemo-preventive, chemotherapeutic activity etc. Phytotherapy i.e., the use of herbal agents as medicines is gaining interest in medicine and dentistry and among these curcumins has played a very vital role, and because of its proved potential for anti-cancer therapy it has now claimed wide attention globally.<sup>3</sup> Turmeric has held an important position in India's traditional Ayurvedic medicine as it was prescribed for treatment of many medical problems ranging from constipation to skin diseases. In Chinese medicines, it is considered to be a bitter digestive and carminative.<sup>4</sup> In Unani, turmeric is considered as blood purifiers and safest herb of choice. It has been demonstrated that curcumin down regulates STE (khaini) or NNK-induced NF- $\kappa$ B and COX-2 in oral premalignant and cancer cells in vitro.<sup>5</sup> Curcumin may suppress or prevent oral pre-cancerous and cancerous lesions and conditions by inhibiting free radicals. In spite of these attractive properties of curcumin, information on the therapeutic efficiency of curcumin has been limited, partly due to its poor oral bio-availability. Curcumin is found to be poorly soluble in water, the maximum solubility of which in aqueous buffer (pH 5.0) was reported to be as low as 11 ng/ml. The limited solubility of curcumin, as well as extensive systemic metabolism, could be responsible for the low bioavailability of curcumin after oral delivery. In addition, curcumin in solution may be sensitive to UV light, and so marked photochemical degradation

could occur under UV exposure, leading to difficulty in its handling for clinical use.<sup>6</sup> Several studies have indicated that the amount of curcumin in the serum after an intake of 4-8 g is only 0.4-3.6  $\mu$ M. The limited literature evidence devoted to show improvements in curcumin bioavailability reveals that the curcumin bioavailability enhancement has not gained significant attention.<sup>7</sup> Here, we review the effect of curcumin on oral health.



## HISTORY

*Curcuma longa* Linn which belongs to the family Zingiberaceae is originated in India.<sup>8</sup> Marco Polo in the year 1280 visited to China & India, where he first mentioned about turmeric in writings. Curcumin was first of all introduced to Europe by Arab trader named Vasco de Gama in the 13th century who in 15th century when visited India introduced spices to the West. When turmeric is combined with other spices it is called as Curry powder. In Asia turmeric is widely used in cookery, as medicine, cosmetics and fabric dyeing for more than 2000 years. The medicinal history of turmeric is approximately 2500 years old. Ayurveda, Unani, Siddha and Chinese medicine recommend turmeric for a numerous disorders and diseases. According to Susruta's Ayurvedic Compendium, dating to 250 BC an ointment containing turmeric can relieve the effects of poisoned

food. In traditional India, the powder form is widely used against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatic disorders, sprains and swellings caused by injury, and sinusitis.<sup>9</sup> The dried rhizome of curcumin can be 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.<sup>10</sup> In both the Ayurveda and Siddha systems of medicine, a turmeric paste has many usages like topical application for ulcers and scabies. Recent emphasis on the use of natural ingredients made researches to do detailed study of curcumin medicinal usage which stated that curcumin has

wide range of benefit antioxidant, chemo preventive and chemotherapeutic effects.<sup>11</sup>

## CHEMISTRY

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-Dione) is the most active polyphenolic constituent, powerful ingredient in the traditional herbal practices.<sup>3</sup> Turmeric is comprised of a group of three curcuminoids: curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins. 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.<sup>4</sup>

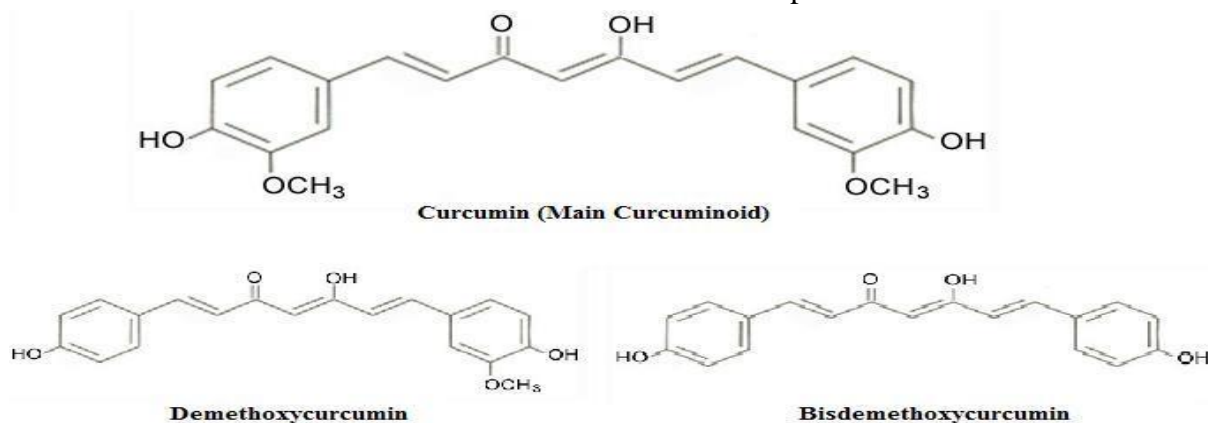


Figure- Structures of Curcumin (Diferuloylmethane), Demethoxycurcumin, and Bisdemethoxycurcumin.

Turmeric includes protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%), moisture (13.1%). The essential oil obtained from the steam distillation of rhizomes has alpha-phellandrene (1%), sabinene (0.6%), cineol (1%), bornoel (0.5%), zingiberene (25%), sesquiterpenes (53%).<sup>3</sup> The components of turmeric are known as curcuminoids comprised of curcumin (diferuloyl methane), demethoxycurcumin and bisdemethoxycurcumin. The melting point of curcumin is 184°C. It is soluble in ethanol and acetone but insoluble in water.

They also exist as keto-enol tautomers. Most recent available preparation of curcumin includes approximately of 77% diferuloylmethane, 18% demethoxycurcumin, 5% bis-demethoxycurcumin.<sup>3</sup>

## PHARMACOLOGICAL ACTIONS OF CURCUMIN

The variety of human disorders against which curcumin has potential has been revealed by

numerous clinical trials. Some of the most important therapeutic effects or actions of curcumin are narrated as under-

### **1. Anti-inflammatory effects-**

Curcumin has the ability to suppress the acute and chronic inflammation. It reduces inflammation by lowering histamine levels and by possibly increasing the production of natural cortisone by adrenal glands. They also reduce pain from arthritis, bursitis, tendonitis, stiffness of joints. It also inhibits the biosynthesis of inflammatory prostaglandins from the arachidonic acid and neutrophil function.<sup>3</sup>

Research shows 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 tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinases. COX-2 and iNOS inhibition are likely accomplished via curcumin's suppression of nuclear factor kappa B (NF- $\kappa$ B) activation. NF- $\kappa$ B, a ubiquitous eukaryotic transcription factor, is involved in regulation of inflammation, cellular proliferation, transformation, and tumorigenesis. Curcumin is thought to suppress NF- $\kappa$ B activation and proinflammatory gene expression by blocking phosphorylation to inhibitory factor I-kappa B kinase (IKB). Suppression of NF- $\kappa$ B activation subsequently down-regulates COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis. In an animal model of inflammation, curcumin also inhibited arachidonic acid metabolism and inflammation in mouse skin epidermis via down-regulation of the cyclooxygenase and lipoxygenase pathways.<sup>4,12,13</sup>

### **2. Anti-oxidant 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 & glutathione peroxidase.<sup>9</sup> The antioxidant mechanism of curcumin is supported by the following reasons:

1. Curcumin is a very effective scavenger of reactive oxygen species.
2. Inhibits oxidative DNA damage.
3. It indirectly acts as antioxidant by enhancing the synthesis of glutathione which is an important intracellular antioxidant.
4. It is involved in oxygen quenching and making it less available for oxidative reactions.
5. Curcumin interacts with oxidative cascade and prevents its outcome.
6. It chelates with iron and disarm the oxidative properties.<sup>10</sup>

Water-and fat-soluble extracts of turmeric and its curcumin component exhibit strong antioxidant activity, comparable to vitamins C and E. A study of ischemia in the feline heart demonstrated that curcumin pre-treatment decreased ischemia induced changes in the heart. Evaluating the outcome of curcumin by an in vitro study on endothelial heme oxygenase-1, an inducible stress protein, which was carried out by utilizing bovine aortic endothelial cells. Incubation (18 h) with curcumin ensued in intensified cellular resistance to oxidative damage.<sup>13</sup>

### **3. Anti-carcinogenic effects-**

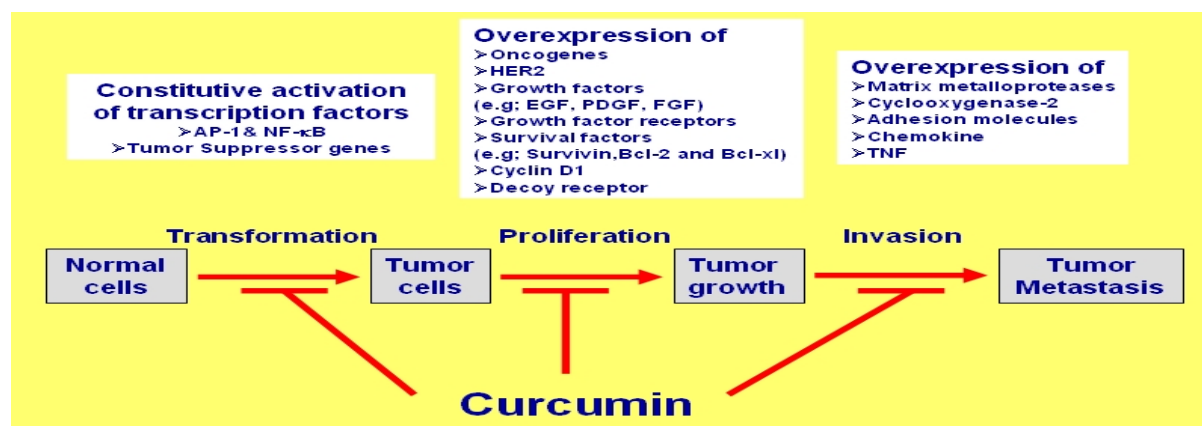
Curcumin potentially helps to prevent the new cancers that are caused by chemotherapy or radiation used to treat existing cancers. It effectively inhibits metastasis (uncontrolled spread)

of melanoma and may be especially useful in deactivating the carcinogens in cigarette smoke and chewing tobacco.<sup>3</sup> Curcumin is an important anticancer agent & it decreases the cancer initiation of skin, mammary gland, oral cavity, and oesophagus. 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 oncogenes, 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 glutathione s transferase activity.<sup>9</sup>

It has a major role in the treatment of various precancerous conditions such as oral submucous fibrosis, leukoplakia, and lichen planus. Turmeric extract and turmeric oil have demonstrated on co-preventive activity in in vitro and

in vivo animal experiments. The local symptoms of burning sensation and pain were reduced, and partial reversal of opening of the mouth was also observed.<sup>11</sup>

Animal studies including rats and mice, also in vitro studies employing human cell lines, have revealed curcumin's potential to hamper carcinogenesis at three stages: tumor promotion, angiogenesis, and tumor growth. Curcumin shows cell proliferation and tumor growth which were studied in colon and prostate cancer. In vitro and in vivo studies Turmeric and curcumin have the ability of repressing the activity of various mutagens and carcinogens in a medley of cell types. Due to direct antioxidant and free-radical scavenging effects turmeric and curcumin produce anti-carcinogenic effect, their capability to indirectly enhance glutathione levels, thereby assisting in hepatic detoxification of mutagens and carcinogens, and hindering nitrosamine formation<sup>13</sup>



#### 4. Anti-microbial effects-

Curcumin and the oil fraction inhibits the growth of variety of bacteria like Streptococci, Staphylococci, Lactobacillus, etc. and also prevents Helicobacter pylori Cag A + strains in vitro. It is also effective against Enterococcus faecalis, and will serve to be useful as root canal medicaments in endodontics. It also acts as an

tifungal agent which is active against Aspergillus flavus, A. parasiticus, Fusarium moniliforme, Penicillium digitatum. It has antiprotozoan activity against E.histolytica, Leishmania, Plasmodium falciparum. It also has antiviral effect which inhibits HIV in test tube studies and also inhibits UV light induced HIV gene expression.<sup>3</sup>



Growth of bacteria, parasites, and pathogenic fungi is hampered by the turmeric extracts and the essential oil of *C. longa*. According to a study uptake of 1% turmeric as a dietary supplement showed improved weight gain and decline in small intestinal lesions in chicks infected with the cecal parasite *Eimeria maxima*. Another study which involved infecting guinea pigs with either dermatophytes, pathogenic molds or yeast revealed that topical application of turmeric oil reticent dermatophytes and pathogenic fungi. Although neither turmeric oil nor curcumin affected the yeast isolates. Dermatophytes and fungi infected guinea pigs showed improvement in the lesions. The lesions disappeared completely after 7 days of applying turmeric. Curcumin possesses moderate activity against *Plasmodium falciparum* and *Leishmania major* organisms.<sup>13</sup>

#### **5. Hepatoprotective effects-**

Turmeric has been found to have a hepatoprotective characteristic similar to silymarin. Animal studies have demonstrated turmeric's hepatoprotective effects from a variety of hepatotoxic insults, including carbon tetrachloride (CCl<sub>4</sub>), galactosamine, acetaminophen (paracetamol), and *Aspergillus*, aflatoxin. In rats with CCl<sub>4</sub>-induced acute and subacute liver injury, curcumin administration significantly decreased liver injury in test animals compared to controls. Turmeric extract inhibited fungal aflatoxin production by 90% when given to ducklings infected with *Aspergillus parasiticus*. Turmeric and curcumin also reversed biliary hyperplasia, fatty changes, and necrosis induced by aflatoxin production.<sup>13</sup>

#### **6. Cardiovascular effects-**

Protective effect of turmeric on the cardiovascular system lowers the triglyceride and cholesterol levels to decline the susceptibility of low-density lipoprotein (LDL) to lipid peroxidation, and hampers platelet aggregation. Even with low doses of turmeric these effects are visible. Triglyceride and cholesterol level decline were observed, but elevated dose did not decline lipid peroxidation of LDL. The reason for Turmeric extract's effect on cholesterol levels may be due to increased transformation of cholesterol to bile acids in the liver and reduced cholesterol uptake in the intestines. Platelet aggregation inhibition by *C. longa* constituents is via potentiation of prostacyclin synthesis and inhibition of thromboxane synthesis.<sup>13</sup>

#### **7. Gastrointestinal effects-**

On the gastrointestinal tract, the constituents of *C. longa* has several beneficial effects. Bicarbonate, pancreatic enzyme, secretin, and gastrin, secretion enhanced by p-tolymethyl carbinol, a turmeric component and intestinal spasm reduced by sodium curcumin. Turmeric is effective in inhibiting ulcers caused by alcohol indomethacin, reserpine, stress, and pyloric ligation, significantly enhancing the gastric wall mucus subjected to these gastrointestinal insults in rats.<sup>13</sup>

#### **8. Photodynamic effects-**

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-Dione) has potential as a photo sensitizer for photodynamic treatment of localised superficial infection in eg: the mouth or skin. In vitro studies reveal that aqueous preparations of curcumin has phototoxic effects against certain bacteria like *Enterococcus faecalis*, *Streptococcus intermedius*, *E. coli*. Also, photo dynamic inactivation of *Candida albicans*

in a murine model of Oral candidiasis has been noted.<sup>3</sup>

### 9. Anti-hyperalgesic effect-

Curcumin has diverse therapeutic effects as anti-oxidant, anti-inflammatory, anti-cancer, etc., it also exhibits anti-hyperalgesic effect. The vanilloid moiety of curcumin is considered most important for activation of the Transient Receptor Potential Vanilloid 1 (TRPV1) which have anti nociceptive effects under behavioural studies and in vitro whole cell patch clamp recordings in the trigeminal system.<sup>3</sup>

### 10. Radio sensitization and radio protection-

An interesting aspect of curcumins activity is the ability to exert both radioprotective effects in normal cells and radiosensitizing effects in cancer cells. 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 downregulation of Bcl-2.<sup>9</sup>

### Dental Applications of Curcumin

The followings are some of the important dental applications of curcumin which are narrated as under-

- A. As dental reliever
- B. Pit and fissure sealant

- C. Dental plaque detection system
- D. Curcumin as an anti-cariogenic agent
- E. Periodontal problems
  - a mouthwash
  - subgingival irrigant
  - local drug delivery system
- F. Precancerous lesions and condition
- G. Recurrent Aphthous stomatitis
- H. Curcumin in reverse smoking

### I. Anti-tumorogenic

Curcumin in dental pain

- Roasted or ground turmeric could be used for massaging aching tooth to provides relief from dental pain and associated swelling.<sup>10,11</sup>

### 2. Curcumin as an anti-cariogenic agent

- The essential oil extracted from *Curcuma longa* has anti-cariogenic property against *Streptococcus mutans* at concentrations from 0.5 to 4 mg/ml.
- It inhibit adherence of *S.mutans* to saliva coated hydroxyl apatite beads.<sup>10,3</sup>

### 3. Curcumin in periodontal problem

- Topical application of 1 tsp of turmeric +1/2 tsp of salt +1/2 tsp mustard oil cures gingivitis.<sup>10</sup>
- In mouthwash 10 mg curcumin extract in 100 ml distilled H<sub>2</sub>O +0.005% peppermint will reduce microbial count and inflammation.<sup>10</sup>
- Local drug delivery system 2 % whole turmeric decreases plaque index, gingival index, improving pocket depth and relative attachment loss. Significant reduction was observed in trypsin – like enzyme activity of “red complex “microorganisms, namely *Bacteroides forsythus*, *Porphyromonas gingivalis* and *Treponema denticola*.<sup>10,3</sup>

- As a subgingival irrigant 1 % curcumin solution is used as anti-inflammatory agent.<sup>10</sup>
- Normal human fibroblasts and microvascular endothelial cells (hMVEC) treated with curcumin was studied using MTT assay and observed that lower doses of curcumin stimulated the proliferation of normal human fibroblasts and hMVED, whereas higher doses inhibited it.<sup>8,11</sup>
- Curcumin treated hPGF cells exhibited maximum apoptosis at 75 $\mu$ M a decrease in cell population and shrinkage of cell size and morphologic alterations in basal cell carcinoma cells after treatment with 50nM curcumin & found cell shrinkage, disappearance of microvilli and appearance of membrane blebbing.<sup>8,11,12</sup>

#### **4. Curcumin in surgical wound healing**

- Curcumine has capacity to work against H<sub>2</sub>O<sub>2</sub> induce damage in human keratinocytes and fibroblasts and thus contributing to wound healing.<sup>10</sup>

#### **5. Curcumin as plaque detection system**

- Dental plaque cannot be seen by naked eyes, so plaque is generally stained with dental plaque staining agents. The dental-plaque detection system contains at least one selected from the yellow pigment of beni-koji, turmeric extracts, and curcumin as dental plaque staining agent and a light-emitting apparatus, having a wavelength within a range of 250 to 500 nm.<sup>8,12</sup>

#### **6. Curcumin as intracanal medicament**

- It has ability to remove smear layer and limited anti-bacterial activity, detrimental effect on dentin macrophages structural integrity, elasticity and flexural strength can be used as an irrigant and intra canal – medicament.<sup>3</sup>

#### **7. Curcumin as Pit and Fissure Sealant**

- It can be applied on surface of tooth for prevention and reduction of dental caries
- Curcumin serves two roles-<sup>11,12</sup>
  - (i) It gives a color tint to the pit and fissure sealant.
  - (ii) Anti-bacterial action.

#### **8. Curcumin in treatment of pre-cancerous lesions and conditions**

- Curcumin increases the local and systemic antioxidant property with significant levels of vitamin C and Vitamin E. It also decreases the lipid peroxidation and DNA damage.<sup>10</sup>
- Oral Lichen Planus: Curcumin has shown immunomodulatory effect involving activation of host macrophages and natural killer cells and modulation of lymphocytes mediated function

#### **ORAL SUBMUCOUS FIBROSIS (OSMF):**

- Cell proliferation in fibroblasts and myofibroblasts is checked.
- Cell cycle arrest in myofibroblasts is inhibited.
- Reduce the Bcl-2/Bax ratio in myofibroblasts and hence induces apoptosis in myofibroblasts.
- Type I and type III collagen in myofibroblasts production is diminished.<sup>10</sup>

#### **9. Curcumin in Recurrent Aphthous Stomatitis**

- Curcumin gel is effective in reducing pain intensity and size of aphthous ulcer.<sup>10,11,12</sup>

#### **10. Curcumin in Reverse smoking**

- Curcumin, as it targets patches, excrescences, red areas and ulcerations produced by reverse smoking.<sup>10</sup>
- Curcumin in oral cancer as a chemopreventive agent-



- a. Effect of curcumin in tumor microenvironment-inhibits FGF induced neovascularisation and also inhibits VEGF and angiopoetin 1 & 2
- b. Effect of curcumin on tumor suppressor gene P53- growth arrest and apoptosis.<sup>9</sup>

Curcumin effects mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis, and metastasis.<sup>13</sup>

### 11. Curcumin as an antiviral agent

- Curcumin is inhibitor of HIV -1PR. It acts by binding to the crystal structure of HIV-1PR and its relative absorbability is responsible for the inactivity of HIV. But research is still under progress.<sup>13</sup>

### SIDE-EFFECT OF CURCUMIN

- Curcumin can induce DNA damage and chromosomal alterations both in vitro and in vivo at concentrations similar to those reported to exert beneficial effect.
- Low concentrations of curcumin induce antioxidant effects, higher concentrations of this compound increase the cellular levels of ROS (reactive oxygen species).
- Curcumin has also been shown to inhibit the activity of the drug-metabolizing enzymes cytochrome P450, glutathione-S-transferase, and UDP glucuronosyltransferase. The inhibition of these enzymes in people taking curcumin may lead to an undesired increase in the plasma concentrations of some drugs and cause toxicity.

### CONCLUSION

The benefits of turmeric include: analgesic, anti-bacterial, anti-inflammatory, anti-tumor, anti-allergic, anti-oxidant, antiseptic, antispasmodic, appetizer, astringent, cardiovascular, carminative, cholagogue, digestive, and diuretic. There are many uses of turmeric in dentistry. The use of plants and herbs for dental

care is a very common indigenous system of medicine and we must include it in our everyday life. Further research is needed for the proper use of turmeric in Dentistry.

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**Source of Support: Nil**

**Conflict Of Interest: None Declared**

How to cite this URL: Hemakeswani Et Al: Curcumin- A Magical Medicine: A Comprehensive Review. *International Ayurvedic Medical Journal* {online} 2017 {cited February, 2017} Available from:

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