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Effectiveness of Curcumin in Oral Diseases: An Update

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ABSTRACT

Oral diseases play a serious challenge to public health around the world. When left untreated, both the mouth and also the remaining the body would be adversely affected by oral diseases. Different treatment modalities are available for various dental diseases, but the most downside of those modern drug treatments are the frequent side effects related to their use. This has contributed to renewing interest in the development of novel plant-derived anti-infective natural compounds. Curcumin is an anti-inflammatory agent that occurs naturally, with different biological and medicinal properties. It has proven anti-inflammatory, antioxidant, antimicrobial, hepato-protective, immuno-stimulant, antiseptic, and anti-mutagenic properties. Due to these properties, it is especially useful in dentistry for the treatment of periodontal diseases and oral cancers. Turmeric can also be utilized in alternative treatments as a pit and fissure sealant, mouthwash and subgingival irrigant. Its gel form can even be used as a local drug delivery system. It is evaluated with a view to mitigate the human diseases, particularly in cancer and its potential to reduce cancer risk. Curcumin has only negligible side effects such as diarrhoea, diarrhoea, allergic skin reaction, gastric pain. The objective of this article is to review the efficacy and therapeutic properties of curcumin in maintaining oral health.

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INTRODUCTION

Oral diseases play a serious challenge to public health around the world. When left untreated, both the mouth and also the remaining the body would be adversely affected by oral diseases. The environment people reside under and their level of exposure to other services and facilities often play a role in the production of oral disease (Hatcher, 2008). Such broader origins behind the cycle of illness need to be discussed to maintain a systematic and successful approach to care.

Oral leukoplakia is a pre - malignant condition that affects the mucous membrane. It is a white patch or accumulation that forms in the oral cavity and is closely correlated with smoking. It is described as a basic oral white mucous cyst that can not be treated like any other quantifiable cyst. Oral lichen planus is a persistent inflammatory recurrent disease that impacts the mucous membranes within the mouth. Oral lichen planus may occur as spots of white, pleated, red, bulged tissue or broken skin (Kuwatada *et al.*, 2017). These injuries can lead to burning, pain or even other soreness.

Oral symptoms arise in 30-80 percent of individuals with HIV, with major differences based on normal antiretroviral treatment (ART) availability. Oral manifestations involve fungal, viral, or bacterial infections, the most prevalent and quite often the first symptom of which is the oral candidiasis. Ulcers of oral HIV provoke pain, discomfort, sore throat and swallowing difficulties (Jamison, 2003).

Oral cancer is a widespread neoplasm especially in Asia and the Pacific Islands. Oral cancer accounts in the United States for 2–4 percent of reported cancers per year. Oral mucosal carcinomas are thought to be primarily triggered by chemical carcinogens while the origin of certain oral neoplasms often includes bacterial, fungal, and physical occurrences (Kou, 2008).

Periodontitis is an inflammatory bacterial infection of the supporting tissues of teeth and is one of the most prevalent diseases occurring in humans. It is a complicated condition wherein the utterance of the disease involves intricate biofilm interactions with host immunoinflammatory response and substantial changes in homeostasis of the bone and connective tissue (Buduneli, 2012). There is thus a discrepancy between virulence of bacteria and the ability to protect the host. The spread and development of the disease are linked to the invasion of chief microorganisms including Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, and Prevotella intermedia (Messadi *et al.*, 2009).

Scaling and root planing (SRP) is among the most widely employed techniques in the management of periodontal diseases that have been used as the "gold standard" for mechanical rehabilitation. Studies have found that scaling and root planing have only limited effects on certain disease-causing organisms, frequently failing to achieve total eradication of subgingival bacteria (Kaur *et al.*, 2017). This could be due to some of these organisms being able to survive in soft tissues, dentinal tubules, or root surface irregularities, thus leading to treatment failure.

Different treatment modalities are available for various dental diseases, but the most downside of those modern drug treatments are the frequent side effects related to their use. This has contributed to renewing interest in the development of novel plant-derived anti-infective natural compounds (Hazarey *et al.*, 2015).

Plants were the primary medical source throughout ancient times. A variety of therapeutic properties have been applied to Turmeric within the conventional medicine framework. Turmeric, a Curcuma longa rhizome, is used in Asian countries as a flavouring agent, medicinal herb, and dye (Ara *et al.*, 2009). And it is a herb recognized by a common man for its different biological and medicinal properties that is a more suitable and profitable choice. It is evaluated with a view to mitigate the human diseases , particularly in cancer and its potential to reduce cancer risk.

In India, where Ayurveda is a natural medicine method, turmeric is used to reinforce and heat the whole body, its paste is used to cure specific eye infections, and to clothe, heal cuts, wounds, acne, and different skin problems (Shubhashree and Bhavya, 2018). It has proven anti-inflammatory, antioxidant, antimicrobial, hepato-protective, immuno-stimulant, antiseptic, and anti-mutagenic properties. Due to these properties, it is especially useful in dentistry for the treatment of periodontal diseases and oral cancers (Sood and Nagpal, 2013).

Curcumin 's recorded efficacy against leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, squamous cell carcinoma of the head and neck, lung cancer, melanoma, neuronal cancers, sarcoma, and oral cancer, illustrates its potential to influence several non - linear goals (Nayak *et al.*, 2008). The current study sums up the most significant innovations of curcumin in the area of oral diseases and also offers fresh understanding of the molecular pathways influencing the dietary polyphenol curcumin's successful anticarcinogenic function.

The main objective of this article is to review the efficacy and therapeutic properties of curcumin in maintaining the oral health and also its effectiveness in the treatment of dental pain, periodontal diseases, oral cancers, and also its usage in various other aspects of dentistry will be discussed in this article.

Effect of Curcumin on Disease Control and Prevention

Curcumin has a vital function in the diagnosis of periodontal disease and oral cancers. This can be used for oral submucous fibrosis therapy, against oral leucoplasia, lichen planus and may also perform an auxiliary function in scaling / root planing for recurrent periodontitis care. Curcumin topical use is effective in managing oral mucositis signs and symptoms and can be used as a mouthwash for the diagnosis of periodontitis. Turmeric can also be utilized in alternative treatments as a pit and fissure sealant, mouthwash and subgingival irrigant. Its gel form can even be used as a local drug delivery system (Perumalsamy, 2018).

Periodontitis treatment

Lipopolysaccharide (LPS) is an essential part in the outer membrane of gram-negative bacteria like P. intermedia. It may activate a variety of host cells to generate and release a broad spectrum of proinflammatory cytokines like Tumor Necrosis Factor - alpha (TNF-α), Interleukin-1 (IL-1), IL-6 and IL-8 tumor necrosis factor. It has been documented that LPS preparations isolated from oral black-pigmented bacteria, including P. intermedia, have specific chemical and immunobiological properties very distinct from those of the Enterobacteriaceae family classical LPSs, such as Escherichia coli and Salmonella. Activation of Ralph And William's 264.7 cells (RAW 264.7 cells) with P. intermedia LPS triggers substantial expansion in the number of IL-6 and can be dose-dependent suppressed by curcumin. Research findings tend to show medicating these cells with 20 ìM curcumin whittled down IL-6 development by 83 percent without affecting cell survival, implying that the cytotoxicity of inhibitory effects of curcumin on IL-6 production was totally irrelevant (Cox and Zoellner, 2008).

Curcumin as a Treatment Modality in Recurrent Aphthous Stomatitis

Recurrent Aphthous Stomatitis (RAS) is an inflammatory disease that attacks the oral mucosa from an uncertain etiology. The disorder includes primarily non keratinized mucosal surfaces and is marked by single or numerous severe ulcers with intermittent healing and recurrence. The emergence of ulcers is accompanied by a prodrome of 24-48 hours of intermittent burning or discomfort. The initial average age is between 10 and 19 years, which will extend throughout adulthood. Studies have indicated that the lesion cured in patients having used traditional antiseptic gel only after a period of time, as in previous assaults. They did not experience premature pain reductions or recurrence frequencies. A few other studies have shown that 10 patients who used curcumin oil disclosed that ulcers began recovering earlier than those in pre - existing ones; pain was also reduced quickly. A one year follow-up in these patients has shown no relapse (Li, 2017).

Influence of Curcumin on Human Gingival Fibroblasts

A variety of experiments have showed apoptosis of human primary gingival fibroblast (hPGF) cells at lower doses, such as 1, 10 and 25μM of curcumin, but at higher doses, such as 50, 60, 75 and 100 μM, strong apoptosis was documented statistically important. They also noticed that even the influence of curcumin controlled normal human fibroblasts and micro-vascular endothelial cells (hMVEC) utilizing MTT test, and reported that low concentrations of curcumin activated normal human fibroblasts and hMVED multiplication, while higher doses impaired it. As per other researchers curcumin treated hPGF cells displayed maximal and substantial cell death at 75μM and saw decrease in cell population and decline in cell size and morphological modifications in basal cell carcinoma cells treated with 50nM curcumin & noticed cell shrinkage, microvilli depletion and membrane blebbing appearance. Curcumin hinders Interleukin-6 development in Prevotella intermedia Lipopolysaccharide-Triggered Raw 264.7 cells (Das *et al.*, 2010).

Dental-Plaque Detection System

Caries as well as periodontal infections are considered to be infectious diseases caused by microbes in dental plaques, and the expulsion of dental plaques is identified to be of great importance for the wellness of oral cavities. Dental plaques, however, are not easily identifiable by the naked human eye and it is difficult to accurately affirm their area of adhesion and prevalence. Likewise, microbial dental plaques are usually stained with dental plaque dyeing agents, that also contain dyes, to disclose their sites to unmask the dental plaques hooked up to them. The dental-plaque detection system involves a dental-plaque dyeing agent constituting one chosen from the beni-koji yellow pigment, turmeric derivatives as well as curcumin; and a light-emitting device producing light with a wavelength of between 250 and 500 nm to an entity in the oral cavity where the dental-plaque staining agent is fitted. Beni-koji and turmeric yellow pigment are regarded as staining agents, and are often used for many purposes (Chainani-Wu, 2003).

Pit and Fissure Sealant

Tinted pit and fissure sealant have been found to be useful for application on tooth surfaces for the reduction or elimination of tooth decay. This sealant may be developed from a formulation consisting of a polymerizable resin system containing acrylic monomer and at least one selected colorant from the Annatto extract, turmeric extract, and Apo-8-Carotenal grouping (Chaturvedi, 2009).

Role of Curcumin as a Subgingival Irrigant

As combined with chlorhexidine and saline unit as an adhesive treatment in patients with periodontitis, curcumin 1 percent as a subgingival irrigant resulted in substantial decrease of bleeding on poking and redness. Positive results produced through irrigation of curcumin can be due to its anti-inflammatory , anti-oxidant effects in reducing inflammation faster than chlorhexidine, which functions mainly as an anti-bacterial. Curcumin functions likely in reducing inflammatory mediators of arachidonic acid production to creatine and creatine as anti-inflammatory products. Curcumin does have a benefit on aspirin, as it specifically prevents prostaglandin E2 and thromboxane synthesis thereby not influencing prostacyclin synthesis. Curcumin decreases inflammatory mediators by means of its anti-inflammatory ability, which induces shrinkage by rising inflammatory oedema which connective tissue vascular engorgement. This also facilitates the proliferation of fibroblasts in the wound bed and contributes to loss of vasculature by inducing connective tissue fibrosis. It facilitates wound healing by inducing a spike in fibronectin and converting transcription of the growth factor L. Curcumin embedded in collagen that serves as a supportive matrix for slow release has also been shown to improve wound healing and promote cellular multiplication (Motterlini *et al.*, 2000).

Curcumin with Oral Cancer

Cancer and inflammation is a recent science area that ranges from simple to therapeutic treatments where the treatment of curcumin has been shown to significantly minimize the occurrence of oral squamous cell carcinoma (SCC).

Curcumin has pleiotropic activities resulting from its diverse composition and its capacity to affect several nonlinear signal transduction, including Nuclear Factor kappaB (NF-kB) regulated survival pathways, Protein kinase B (PKB), Nuclear factor erythroid related factor 2 (Nrf2) dependent growth factors and cytoprotective pathways and also metastatic and angiogenic processes. Curcumin is often an oxygen radicals contributor to radical scavenger and hydrogen, which has both pro as well as antioxidant involvement. Also it bonds metals, especially iron and copper, and may act as an iron chelating agent. Curcumin is a relatively low toxic material, and its bioavailability is minimal (Chaudhari, 2011). A minimum degree of curcumin quantities which can be reached physiologically is appropriate for its chemotherapeutic and chemopreventive activities. Curcumin often controls several goals (multitargeted therapy), which are required to cure certain illnesses, is affordable and has been shown to be effective in clinical trials for humans.

Molecular Mechanism of Curcumin on Oral Cancer

Curcumin inhibits oral cancer by multiple pathways as seen in numerous research, as mentioned here. Curcumin decreased the proliferation and invasion of SCC-25 cells by inhibiting the phosphorylation of the Akt, Extracellular signal regulated kinase $\frac{1}{2}$ (ERK1/2) and Signal transducer and activator of transcription 3 (STAT3) downstream signaling molecules (Xu *et al.*, 2020). Certain studies showed that curcumin prevented proliferation of SCC-25 cells and caused dose-dependent step arrest of G2 / M (Yin, 2020). This also blocked infiltration of SCC-25 cells and downregulated expression of matrix metalloproteinase 2 (MMP-2), MMP-9, Urokinase plasminogen activator (uPA) and Urokinase plasminogen activator Receptor (uPAR) in oral cancer control (Zhao, 2019).

Curcumin has the capacity for anti-cancer in oral squamous cell carcinoma dependent on the expression of the nuclear factor kappa B and cyclooxygenase 2 through epithelial dysplasia (Maulina, 2019). Cetuximab and the mixture of curcumin mediated apoptosis and significantly improved caspase-3 and caspase-9 behaviors relative to solitary therapy demonstrated oral anticancer results. The protein expression levels of Epidermal Growth Factor Receptor (EGFR) and Mitogen-activated protein kinase (MAPKs) were also significantly reduced by combination therapy (Chen, 2018).

A group of OSCC cell lines originating from oral cancer patients compares the intracellular copper rates and exposure to curcumin therapy. Increased level of copper in OSCC cells treated with curcumin was accompanied by induction of intracellular Reactive oxygen species (ROS) and increased level of Nrf2 that controls oxidative stress responses in cells. Initial apoptosis was found in combination therapy but not in curcumin or copper-only care (Lee, 2016). Curcumin minimizes drug resistance by blocking Epithelial Mesenchymal Transition (EMT), thus encouraging traditional chemotherapeutic antiproliferative effects. Curcumin thereby has the ability being used as a new adjunctive factor to avoid tumour progression and can at least be due in part to its hindering of the EMT cycle (Bahrami *et al.*, 2019).

Curcumin is also a selective stimulator for the treatment of leukoplakia by NF-kB/ Cyclooxygenase-2 (COX-2), molecules disrupted in oral carcinogenesis (Kuriakose, 2016). Olaparib including curcumin combination improved the mortality of oral cancer cells not only by inducing the DNA harm but also by preventing Base excision repair (BER) operation initiation (Nile, 2016).

Curcumin systemic administration has a chemopreventive function that is caused by 4-nitroquinoline-1-oxide (4-NQO) during oral carcinogenesis (Gonçalves and De, 2015). In the existence of N-acetylcysteine (NAC), an antioxidant, curcumin-induced reactive oxygen species (ROS) development and autophagic vacuole formation by curcumin are almost fully prevented. Curcumin also demonstrates antitumor action against OSCC, both through autophagy and apoptosis (Lee *et al.*, 2018). Curcumin disrupted Hepatocyte growth factor (HGF) induced EMT and motility of cells in Hematopoietic stem cells-4 (HSC-4) and Ca9-22 by c-Met inhibition. These results thus identify curcumin as a replacement medication for treatment with OSCC (Ohnishi, 2020).

Nanoformulated medication (curcumin-SiNp complex) was formulated in SiNp via post-loading curcumin, and the compound was soluble in an aqueous mixture. Cellular absorption tested by fluorescence microscopy and spectroscopy revealed that even when cells were incubated with curcumin-SiNp complex apart from free curcumin, the concentration of curcumin was greater (Singh *et al.*, 2014). Quantity of curcumin kept in the mucosa indicates the likelihood of the medication having a local effect. In vitro experiments found that free curcumin and curcumin primed to chitosan-coated nanoparticles induced a substantial decrease in intensity and time-dependent survival of SCC-9 human oral cancer cells (Mazzarino, 2015). Curcumin can impair NF-kappaB induction in premalignant oral and cancer cells. Visibility of premalignant oral cells and cancer cells to curcumin culminated in a substantial reduction in cell feasibility and initiated cell death (Sharma, 2006).

Curcumin blocked the multiplication of OSCC cells (SCC-9 cells) by increasing MicroRNA-9 (miR-9) function and decreased the signalling of Wnt (Wingless/Integrated) / β-catenin by growing the production rates of Glycogen Synthase Kinase-3β (GSK-3β), phosphorylated GSK-3β and β-catenin and by reducing the cycline level D1 (Xiao, 2014). Curcumin hindering impact on EGF-induced phosphorylation and intrusion of SCC-25 cells. Certain findings found that curcumin prevented the multiplication of SCC-25 cells which caused the dose-dependent arrest of the step G2 / M (Zhen, 2014).

The mixture of curcumin and irradiation had a synergistic influence- the greatest cell viability results were reported in the tested cell line with a curcumin concentration of 3.75 μM and 5 Gy of irradiation. Curcumin regulates the complex reciprocal relationship between tumour cells and cancer associated fibroblasts (CAFs). Standard and 2 μM Curcumin-treated culturing was conducted for 4 days, accompanied by tumour cell invasiveness evaluation, EMT-marker mRNA / protein expression and facilitators (Salehi, 2019).

Adverse Effects

It has its own negligible side effects such as diarrhoea, diarrhoea, allergic skin reaction, gastric pain (Ashwini *et al.*, 2017), stomach discomfort and even anti-thrombosis function that interferes with blood clot development, given the usage of curcumin in the treatment of most of the oral disorders (Lakshmi *et al.*, 2015).

Future Scope

From this polypharmacological point of view, curcumin must be examined in order to further grasp the pharmacokinetics and pharmacology of each isolated curcuminoid (Gheena and Ezhilarasan, 2019). This compartmentalized knowledge is likely to help us enhance the selective use of curcumin-based research strategies (Sharma *et al.*, 2019). It can also help boost the hiding synergistic potential within the natural extract that can be released by man-made drug designs that require varying the analogous proportions of curcuminoids within the treatment dependent on curcumin (Ezhilarasan *et al.*, 2017b).

For certain research, it is well known that the drawbacks of bioavailability with hydrophobic curcumin are possible but this is offset by studies suggesting otherwise (Perumalsamy, 2018). Commercially motivated arguments that the curcuminoid's hydrophobic existence and its loss of solubility in aqueous media are merely baseless triggers of curcumin bioavailability limitation (Mehta, 2019). Even for some displaying low serum curcumin after a strong oral dose, the pharmacological effects encountered by subjects obtaining curcumin remain challenging to understand (Ezhilarasan *et al.*, 2017a).

Serum curcumin rates are not considered to be adequately important to justify therapeutic effects in some experiments, however, as has been seen in other research, serum curcumin with properly extracted unmodified curcumin extracts may be important and effective (Ezhilarasan, 2018). Given the difficulties, however, in vivo outcomes from one curcumin-based drug to another will vary from therapeutically excellent to average (Ashwini *et al.*, 2017). This indicates that there are other factors which play pharmacological roles and also contribute behaviour (Menon, 2018).

"Curcumin" is a term that is also used to identify the extract of curcumin comprising all three curcuminoids: curcumin I, curcumin II and curcumin II (Rajeshkumar and Kumar, 2018). Confusingly though, as mentioned, "curcumin" is often used on a label to identify curcumin I (Karthiga *et al.*, 2018). In commercial and research applications it must be established as a standard that description to anyone as well as three of the curcuminoids may be qualified by naming the specific curcuminoids (Rajeshkumar *et al.*, 2018). This etymology precision will be established internationally to remain applicable in the area of health care like peer-reviewed literature on label statements on consumable goods, chemotherapy drugs, and scientific papers (Ashwini *et al.*, 2017).

CONCLUSION

Effectiveness of Curcumin in maintaining the oral health and also its treatment of dental pain, periodontal diseases, oral cancers, and also its usage in various other aspects of dentistry were found to have numerous positive effects. Treatment of oral diseases with curcumin in various clinical studies was well tolerated and demonstrated durable and significant with meagre side effects. Thus, the results significantly imply that the effectiveness of curcumin can be taken into consideration and can be applied to improvise the treatment strategies of oral diseases in dentistry.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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