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A Focus on Curcumin Local Application in Oral Diseases Management: Mini Review

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Abstract : *Nutraceutical is a food or à food ingredient that provides medical and health benefits. Polyphenols play an important role in the maintenance of health and prevention of diseases. Among polyphenols, the most widely used substance Curcumin. Curcumin derived from the herbal remedy and dietary spice turmeric. It possesses wide range of beneficial properties includes anti-inflammatory, anti-oxidant, anti-microbial and anti-cancer properties following oral or topical administration, so it can be useful for both systemic and local disease treatments. Local drug delivery provides a more targeted and efficient drug-delivery option than systemic delivery. This review primarily focuses on some of the evidences on local therapeutic approaches of Curcumin for most common oral diseases; oral infection, periodontal diseases, aphthous ulcers, precancerous lesions and oral mucositis. This review also highlights the recent advances of nanocarriers' delivery systems in enhancing and improving the local efficacy of Curcumin to combat specifically some of the oral diseases.*

Keywords –*curcumin, local therapeutic, nutraceuticals, nanocarriers, oral diseases*

I. INTRODUCTION

Nutraceutical is a combination of the words ''nutrition'' and ''pharmaceutical''. It refers to any substance considered to be a food or a food ingredient that provides medical and health benefits. A number of nutraceuticals have been identified during the past decade[1]. Knowledge and use of plants as herbal medicines have occurred in various populations throughout human evolution, beginning when man was learning to select plants for food, and to relieve ailments and diseases[2]. Polyphenols are a group of phytochemicals that are rich sources for anti-oxidants. Polyphenols play an important role in the maintenance of health and prevention of diseases. Among polyphenols, the most widely used substance; Curcumin (***Turmeric***) the herbal remedy and dietary spice. Curcumin is considered a safe, non-toxic and effective alternative for many traditional drugs because of its effects on various systems and therapeutic properties.

Local drug delivery may provide a more targeted and efficient drug-delivery option than systemic delivery for diseases of the oral mucosa. Oral diseases can be effectively treated by local therapeutic approaches, due to the ease of the oral cavity accessibility.

Sankar and *co authors* have reviewed the most common mucosal diseases and identified the current treatment approaches systemically and locally. In addition, they identified the novel biological therapies such as macromolecular biological drugs, peptides and gene therapy which may be of value in the treatment of many chronic oral conditions and if their delivery can be optimized [3].

This review will focus on some of the evidence on local therapeutic approaches of Curcumin for most common oral diseases; oral infection, periodontal diseases, aphthous ulcers, precancerous lesions and mucositis. In addition, exploring the recent advances of nanocarriers' delivery systems in enhancing and improving the local efficacy of Curcumin to combat specifically some of the oral diseases.

1.1. Oral Mucosa Structure and Characteristics

Oral mucosa is a highly diverse, dynamic and responsive environment that despite high accessibility presents a number of challenges for oral drug delivery [4]. As a route of administration, it shows several advantages, where drugs are self-administrable and well accepted by patients. The oral mucosa is easily accessible and rapidly repairs itself after damage or trauma. This short recovery time limits potential adverse side effects caused by long-term topical drug delivery. In addition, there are fewer Langerhans cells in the oral mucosa than the skin reducing the risk of an allergic response [3].

Oral mucosa is a stratified squamous epithelium 40–50 cell layers thick similar to stratified squamous epithelia found in the rest of the body. It has a mitotically active, basal cell layer highly proliferating keratinocytes that proliferate rapidly to repair and replenish epithelial cells which differentiate and eventually shed as the cells become more superficial[5, 6].The basal keratinocytes separatea connective tissue component. Superficial to these are the partially differentiated supra-basal cells (**Fig** 1). The keratinized regions of the oral cavity are gingivae and hard palate [7, 8]. Being a barrier-like between all soft tissues and the environment, oral mucosa helps retaining tissue fluids and excluding extrinsic materials. The main permeability barrier to external materials is in the lower to middle third of the epithelium.

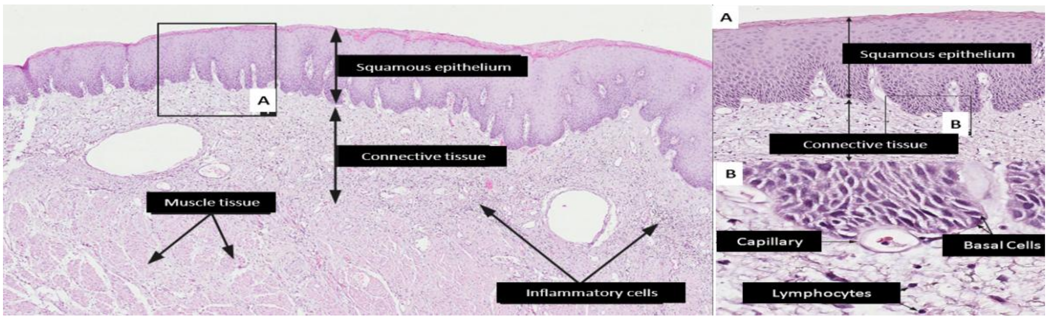

Figure 1: Histological section in normal oral mucosal tissue[9]

The oral mucosa has a small surface area compared to skin and limited exposure time making this delivery route most appropriate for drugs exhibiting high therapeutic potency at relatively small doses. In addition to the impact of salivation, mastication and speech where the constant washing of the oral cavity by saliva limits the mucosal exposure time to the therapeutic agent both, by diluting the drug in the oral cavity, and by clearance of drug into the gastrointestinal tract upon swallowing. Furthermore, constant salivary scavenging within the oral cavity makes it very difficult for dosage forms to be retained for an extended period of time [10, 11]. Saliva, however, can be regarded beneficial in providing a highly hydrated environment in which drugs dissolve and can be well distributed around the entire oral cavity. Mastication, the action of chewing food, can both hinder and enhance drug delivery in the oral cavity. It can also cause damage to or loss of mucoadhesive drug delivery system but it can also be utilized by loading drugs into chewing gum, which are released when the gum is chewed [12].

Oral mucosal delivery has the potential to treat many different conditions and diseases. Each therapy requires distinct penetration and drug retention profiles in order to optimize treatment and minimize side effects.

1.2. Oral diseases

1.2.1. Infections

The oral cavity is a natural habitat for large numbers of microbes, thus must be capable of distinguishing between those that are beneficial or a virulent and those that will invade and cause disease. This ecological niche can act as a reservoir for opportunistic and pathogenic microorganisms that can pose a risk for cross contamination and infection and may even cause systemic infections[13]. It is of a particular importance in case of routine dental practice, as the risk of exposure to microorganisms in the oral cavity is increased due to the open and invasive nature of the procedures.

1.2.2. Aphthous ulcers

Aphthous ulcers are among the most common oral lesions in the general population, with a frequency of 5–25% and three month recurrence rates as high as 50%. Aphthous ulcers have been reported in 2–4% of HIV-seropositive patients, although these patients suffer from larger and more frequent aphthae in advanced stages of their disease[14]. Aphthous ulcers are round or oval, with a grayish yellow, crateriform base surrounded by an erythematous halo of inflamed mucosa. For 24–48 hours preceding the appearance of an ulcer, most patients have a pricking or burning sensation in the affected area. The ulcer usually occurs on the non keratinized oral mucosa. The cause of ulcers is unknown, usually the predisposing factors include genetics, stress, hormonal changes, and immunological disorders[15]. Due to the undetermined etiology of ulcer formation, there is no definite treatment and mainly treatment aimed at relieving the symptoms [16].

1.2.3. Periodontal disease

Periodontal disease is defined as chronic inflammatory condition characterized by the destruction of the periodontal tissues causing loss of connective tissue attachment, loss of alveolar bone, and the formation of pathological pockets around the diseased teeth. It is estimated that over 47 % of adults over 30 years old have periodontitis [17]. Some of these diseases are caused by the accumulation of dental plaque that extends into the subgingival areas of the periodontium [18]. Dental plaque contains pathogenic bacteria that are responsible for the inflammation seen in these diseases. It is known that plaque growth and inflammation of gingival tissue (gingivitis) are strongly linked irrespective of age, gender, or ethnicity [19]. The clinical signs of periodontitis

include changes in the morphology of the affected gingival tissue, which causes the formation of a periodontal pocket. If the disease is left untreated, it can cause loosening and loss of teeth[17].
Periodontal treatment aims to cure inflamed tissue, reduce the number of pathogenic bacteria and eliminate the diseased pockets. Mechanical therapy, chemotherapy and systemic administration of antibiotics are some of the clinical methods being utilized currently.

1.2.4. Potentially malignant oral disease and oral cancer

Potentially malignant oral disease is morphologically altered tissue that is present on clinical examination in which cancer is more likely to occur than in normal tissue. Examples include ***leukoplakia***, ***erythroplakia*** or ***oral lichen planus***. These lesions could be premalignant and exhibit dysplasia on histopathological examination [20].
The overall risk for malignant transformation in oral dysplastic lesions is approximately 20%. Approximately, 90% of oral cancers are squamous cell carcinomas. Potentially malignant disorders of the oral cavity can be broadly classified into precancerous lesions and precancerous conditions. The purpose of identifying potentially malignant disorders of the oral cavity is to initiate timely and adequate intervention and, where possible, to prevent malignant transformation, or enable early diagnosis of malignancy, of these lesions, the mostly prevalent is the oral leukoplakia [3].

Oral leukoplakia (OL) is broadly classified into homogeneous and non-homogeneous subtypes. Homogeneous plaques are predominantly white, of uniform flat, thin appearance with shallow cracks of surface keratin, and have a smooth, wrinkled, or corrugated surface with a consistent texture throughout. On the other hand, non-homogeneous plaques are predominantly white, or white and red (erosive leukoplakia, erythroleukoplakia) and may be either irregularly flat, nodular (speckled), or verrucous. Proliferative verrucous oral leukoplakia is a subtype of verrucous leukoplakia, and is characterized by a multifocal presentation, resistance to treatment, and is of high rate of malignant transformation [21]. A report by Warnakulasuriya[22] proposed that: “OL should be used to recognize white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer”(**Fig.2**)

Figure 2: Oral Leukoplakia (OL)**[23]**

Much of the published data on the prevalence of potentially malignant disorders varies by the geographical location and population studied. The estimates of the global prevalence of oral leukoplakia range from 0.5 to 3.4%. The point prevalence is estimated to be 2.6% with a reported malignant transformation rate that ranges from 0.13 to 17.5%[21]. Besides smoking, the most commonly associated etiological factor, other possible factors such as alcohol, Human papilloma virus (HPV) infection, candidiasis, and reduced concentrations of serum vitamin A and beta-carotene are also proposed[20].

Oral erythroplakia (OE) has long been considered the oral mucosal lesion with the greatest potential for malignant transformation in the mouth. OE is defined as "A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease". It is generally accepted that OE is much less common than OL. Oral erythroplakia mainly occurs in the middle aged and the elderly. Recently it has been stated that OE occurs mostly in men. Oral erythroplakias have been shown to have the highest risk for malignant transformation and therefore early effective treatment of such lesions is mandatory[22].

Oral lichen planus (OLP) is a chronic inflammatory disease that involves skin and mucosa characterized by relapses and remissions. It is one of the most common oral diseases that manifest itself in the oral cavity [24].
The cause of the OLP is not well understood; although cell mediated immunity appears to play a major role in the pathogenesis of OLP it may be possibly initiated by the endogenous or exogenous factors in persons with a genetic predisposition to the development of LP [25].
Treatment of oral dysplastic lesions includes surgical intervention and the use of chemopreventive agents. The treatment for oral squamous cell carcinomas may include single or combination modality surgery, radiotherapy,

or chemotherapy[26]. Oral carcinogenesis has been better understood, thus, it is now possible to target various operational mutations and aberrant molecular pathways. One targeted agent has been approved for the treatment of squamous cell carcinomas; cetuximab, an epidermal growth factor receptor antagonist, and several other agents are under development. Preventive activities, such as risk factor cessation coupled with close surveillance following treatment, are of paramount importance given the high rate of recurrent or new disease.

1.2.5. Mucositis

Mucositis is the painful inflammation and ulceration of the mucous membrane, usually as an adverse effect of chemotherapy and radiotherapy treatment for cancer. Chemotherapy-induced oral mucositis causes the mucosal lining of the mouth to atrophy and break down forming ulcers and affects almost all patients undergoing high dose chemotherapy. Ulcerative oral mucositis is typically painful and affects oral functions including speech, and oral intake of food and medications, thus impacting the quality of life.

1.3. Phytotherapy

The use of herbal agents as medicines (Phytochemicals) is gaining interest in medicine and dentistry. Phytochemicals are naturally occurring substances found in plants. In the past few years the use of phytochemicals derived from dietary components to combat human diseases has gained much attention and considerable public and scientific interest. One very widely used home remedy which has been an area of focus in medicine is turmeric (Curcuma longa).

1.3.1. Curcumin

A special interest has been shed on the natural gift, the golden pigment from the golden spice, ***Curcumin*** (CUR). The dried ground rhizome of the perennial herb Curcuma longa Linn, called turmeric in English, haldi in Hindi and ukon in Japanese, has been used in Asian medicine since the second millennium BC. Its utility is referred to in the ancient Hindu scripture, the Ayurveda. Curcumin, having nearly a two centuries old scientific history, is still attracting researchers from all over the world. Starting from 1815, when curcumin was first isolated from turmeric, there were only a few reports till the 1970s on its chemical structure, synthesis, biochemical and antioxidant activity [27, 28]. However after the report by Singh and Aggarwal [29] in the mid-nineties on its potential anticancer effect, the pace of curcumin research has grown rapidly, with thousands of citations on curcumin to date studying its antioxidant[28], anti-inflammatory[1], antimicrobial[30], cancer chemopreventive and potentially chemotherapeutic properties[31]. While the majority of researchers have been pursuing the biological aspects, few others were interested in understanding the important chemistry of curcumin behind its unique biological activity. In addition to its aromatic, stimulant and colouring properties in the diet, turmeric is mixed with other natural compounds such as slaked lime and has been used topically as a treatment for wounds, inflammation and tumors [32].

1.3.2. Curcumin limitations and approaches

Curcumin suffers limitations that hold it back from clinical application such as low solubility, rapid metabolism, and hence low bioavailability [33]. All of which have limited the therapeutic success of curcumin in cell culture systems and elicited only limited success in various animal and clinical studies[34-37]. In the last two decades, the applicability of several novel drug delivery systems such as micelles, liposomal vesicles, nanoparticles, nanoemulsions, phospholipid complexes and polymeric implants to enhance the bioavailability of curcumin and to enable use of this compound for therapeutic prevention or risk reduction at the precancerous stage has been investigated [31].Various strategies have been taken to overcome the limitations of the use of curcumin and to allow its therapeutic application, including the incorporation in delivery systems [31, 38-40].Using different drug delivery systems based on nanotechnology, such as polymeric nanoparticles, solid lipid nanoparticles (SLN), liquid crystal systems, precursor systems for liquid crystals, liposomes, and microemulsions, is an interesting approach to improve a formulation's most desirable properties. Furthermore, nanoscale particles may represent a future where activity is ensured, and the problems associated with using medicinal plants are overcome[2].

II. LITERATURE REVIEW

2.1. Curcumin and Aphthous Ulcers

Manifar *et al* [41]has studied a randomized, two weeks double blind clinical study on patients between 18 and 65 years old, with minor Aphthous ulcers. Twenty eight- patients were randomly allocated to Curcumin gel containing (2% Curcumin) and 29 patients were allocated to placebo gel. The patients used the medication twice per day using a swap. After enrolment, the size of ulcers were measured by the investigator, and pain was evaluated by the patients based on Perceived Pain Rating Scale before drug application (day 0) and at days 4, 7, and 14. Patients overall satisfaction were assessed at the end of treatment. The results have shown that Curcumin gel significantly reduced pain intensity and size of aphthous ulcer compare to placebo.

Antharjanm and Balan [42] have also reported a case that 10 patients who used *curcumin* oil, ulcers started healing earlier than in previous attacks and there was also early reduction in pain. A follow up for one year has shown no recurrence in these patients. Whereas, patients who used conventional antiseptic gel. The lesion healed only after the period of time as in previous attacks. In addition, no early reduction in pain or frequency of recurrence was observed.

It is worth mentioning that Curcumin local effect in buccal conditions is largely hindered by its extremely limited water solubility, and its hydrolytic degradation in the salivary pH. A study was reported by Nasra *et al* [43]aiming to develop buccal mucoadhesive tablets of curcumin with accepted release and stability at salivary pH. Chemical stability in phosphate buffer saline (PBS) pH 6.8 was tested using a group of stabilizers of which sodium lauryl sulfate (SLS) proved to be the most suitable. In addition, different muccoadhesive tablets formulations were prepared by direct compression technique using a mixture of Hydroxypropyl methylcellulose and Carboxymethylcelluose sodium in different ratios with or without SLS as stabilizer, curcumin as pure untreated drug or in the form of rapidly dissolving solid dispersion (SD) with PVP (Kollidon®25) was examined. The results revealed that the best mucoadhesive performance and *in vitro* sustained release profile(70% released over 12 hours) were exhibited by tablets containing HPMC.K15M: CMC sodium (5:1), SD (1:3) with 15 mg SLS. Salivary concentration was significantly increased compared to undetectable concentration for pure curcumin due to poor solubility and SD without SLS due to hydrolytic degradation. Preliminary clinical study revealed an excellent anti-inflammatory and healing ulcers effect. Therefore Curcumin in this delivery system is proofed to be an excellent candidate for local buccal delivery.

2.2. Curcumin and Periodontal diseases

The anti inflammatory property of curcumin has been studied and demonstrated significant reduction of inflammation. Numerous studies [44-46] have demonstrated that Turmeric mouthwash can be effectively used as an adjunct to mechanical plaque control in prevention of dental plaque and gingivitis in dentistry applications. Turmeric mouthwash was biocompatible and was well accepted by all the subjects without any side effects.

Behal *et al* [47]conducted a split-mouth clinical study design on 30 subjects with chronic localized or generalized periodontitis with pocket depth of 5-7 mm. Control sites received scaling and root planning [SRP] alone, while experimental sites received SRP plus 2% whole turmeric gel. Both groups demonstrated statistically significant reduction in plaque index, gingival index, sulcus bleeding index, probing pocket depth, and gain in relative attachment loss. Greater reduction was observed in all parameters in the experimental group in comparison to those in the control group. The authors concluded that local drug delivery system containing 2% whole turmeric gel can be used as an adjunct to scaling and root planning. Comparable results and conclusion was reported by Anuradha *et al* [48].

Similarly, Merline *et al* [49] clinical study has shown that applications of Curcumin gel has reduced gingival inflammatory signs and promote healing with reduced pocket depth superior than the widely used metronidazole gel medicament. Whereas in a study conducted by Suhag *et al* [50], periodontal sites were treated on day 0 (baseline) by a single episode of scaling and root planning. Subsequently selected sites were irrigated (triple irrigation regimen) with saline (0.9%), chlorhexidine (0.2%), curcumin (1%), or served as non irrigated control sites on day 0 (baseline) immediately following instrumentation. Triple irrigation regimen was repeated for the next 5 consecutive days and on days 15 and 21. Clinical parameters recorded were probing pocket depth (PPD), bleeding on probing (BOP), and redness for 200 sites in 20 patients with chronic periodontitis. The results indicated that the irrigated sites had significant improvement in all parameters as compared with the non irrigated sites on days 2, 3, 4, and 5. The curcumin group showed significant reduction in BOP (100%) and redness (96%) when compared with the chlorhexidine group and saline group on day 5. However, the difference between groups was not significant at the next recall visits. Mean PPD reduction was significantly greater for the curcumin group than all other groups on all post-treatment days. Thus, 1% curcumin solution can cause better resolution of inflammatory signs than chlorhexidine and saline irrigation as a subgingival irrigant.

A new promising approach has been reported by Mazzarino and *co authors* [51].The authors developed mucoadhesive films containing nanoparticles loaded with Curcumin aiming to prolong the residence time of the dosage form in the oral cavity. In addition to increase drug absorption through the buccal mucosa for the treatment of periodontal diseases that requires a sustained drug delivery. Curcumin-loaded nanoparticles were uniformly distributed on the film surface, as evidenced by atomic force microscopy and high-resolution field-emission gun scanning electron microscopy (FEG-SEM) images. In addition, films proved to have a good rate of hydration in simulated saliva solution, displaying a maximum swelling of around 80% and *in vitro* prolonged-controlled delivery of curcumin.

Gottumukkla *et al* [52] described a comparative study to evaluate the therapeutic efficacy of gold standard chlorhexidine (CHX) chips (Periocol-CG) and the developed local drug delivery module, indigenous curcumin

(CU) based collagen as adjuncts to scaling and root planning in the nonsurgical management of chronic periodontitis. The clinical parameters - plaque index, gingival index, probing pocket depth (PPD), and clinical attachment level (CAL) of the selected target site were recorded prior to the placement of the drug at baseline, 1, 3 and 6 months post operatively. Subgingival plaque was analyzed for periodonto-pathicanerobic microorganisms from the samples collected from the selected sites by using BANA reagent strip. The results demonstrated that, both the groups (CHX and CU) produced a significant reduction in all the clinical and microbiological parameters. However, at the end of the study period, CHX group showed greater improvement.

1.4. Curcumin and Oral Infections

The most commonly used anti-microbial formulations include therapeutic agents; which suffer serious side effects, in addition to resistance shown by microorganisms. This is the most common problem encountered in managing oral infection and is related primarily to systemic drug therapy. The lack of antibiotics with minimal or no adverse effects potentiates the need for integrating herbal medicine into pharmaceutical formulation to cover such shortage.

Combination of herbal medicine with nanotechnology has been widely proposed, as nanostructured systems might be able to potentiate the action of plant extracts, reducing the required dose, side effects, and improving activity. In the study of Hazzah *et al* [53], the results have revealed that loading Curcumin into solid lipid nanoparticles (CurSLN) not only maintained its stability, but it also increased its antimicrobial activity, as being in the nanosize range allows more contact with the pathogenic cells, allowing more interaction and therapeutic response. CurSLN showed a higher antimicrobial activity as compared with Curcumin raw material and chemically stabilized Curcumin. Where it showed an increase in its anti microbial activity expressed as MIC by eightfold, fourfold, fourfold, twofold, twofold, and twofold against *Staphylococcus aureus*, *Streptococcus mutans*, *Viridanstrept*, *Escherichia coli*, *Lactobacillus acidophilus*, and *Candida albicans*, respectively.

Mali *et al* [44], compared clinically the anti-microbial activity of 0.1% Turmeric mouthwash against 0.2% chlorhexidine gluconate. The turmeric mouthwash was acceptable in taste. The results revealed that both tested mouthwashes can be effectively used as an adjunct to mechanical plaque control in prevention of plaque and gingivitis. Both mouthwashes have comparable anti-plaque, anti-inflammatory, and anti-microbial properties. Turmeric mouthwash was biocompatible and well accepted by all the subjects without side effects. Similar results was revealed by Nandini and *co authors* [54]. Moreover, Drake *et al* [55] studied the antibacterial effect of curcumin. Bacterial colonies were inoculated into tryptic soya broth enriched cultures. The results showed that curcumin inhibits the growth of C. gingivalis and P. melanogenica.

1.5. Curcumin and Precancerous lesions

Oral lesions are regarded the most challenging in oral medicine practice. They are often chronic, intensely painful and can spontaneously remit, consequently hindering normal day life activities [56].

The easy access to the lesion allows the use of local delivery formulations to directly treat the disease without causing adverse side effects. These lesions are currently managed by invasive surgery and approximately one-third of these lesions will reoccur after surgery [57].

It is worth mentioning that Curcumin has a beneficial role in the treatment of various precancerous conditions like oral submucous fibrosis, leukoplakia and oral lichen planus. Turmeric extract and oil have demonstrated oncopreventive activity in *in vitro* and *in vivo* animal experiments [58, 59]. Most of the recent studies have showed its activity in systemic approaches [60, 61]. Rai *et al* [62] previously reported curcumin efficacy when given orally for treatment of precancerous lesions at a dose as high as 8 g/day. The results showed that 25 patients with oral Leukoplakia, showed significant symptomatic relief and also reduction in clinical size of the lesion by treatment with curcumin. Curcumin increased the local level of vitamin C and E, while it decreased lipid peroxidation and DNA damage for patient suffered precancerous lesions, which suggested that the anti-precancerous effect is through the anti-oxidant and pro-oxidant pathways.

Chainani-Wu *et al* [63] reported that Curcuminoids at doses of 6000 mg/d in 3 divided doses were well tolerated and could prove efficacy in controlling signs and symptoms of oral Lichen planus.

Recently, it has been evidently reported that Curcumin treatment of co-culture between oral squamous cell carcinoma (SCC-25cells) and periodontal ligament fibroblasts (PDL) resulted in decrease of tumor cell migration and invasivity, reversal of epithelial-to-mesenchymal transition (EMT) in tumor cells and decrease of the EMT mediators' gene expression and synthesis in fibroblasts which confirms the palliative potential of Curcumin in clinical application[64].

Very few researches have shown the efficacy of curcumin as targeted local drug delivery in precancerous lesions. Kuttan *et al* [65] examined an ethanolic extract of turmeric as well as an ointment of Curcumin. Both formulae found to produce a remarkable symptomatic relief in patients with external cancerous lesions. Reduction in smell was observed in 90% of the cases and reduction in itching in almost all cases. Dry lesions were observed in 70% of the cases, and a small number of patients (10%) had a reduction in lesion size and pain. In many patients the effect continued for several months. An adverse reaction was noticed in only one of the 62 patients evaluated. However the report is lacking the control group and standard method of Curcumin preparation.

Clark *et al* [66] demonstrated that Curcumin significantly inhibited migration and perforation of squamous cell carcinoma, Curcumin has growth inhibitory effects and prevents tumor formation in an oral carcinogen-induced model at a dose of 15 mg/day.

Recent developments in the field of buccal drug delivery show an increased interest toward nano buccal drug delivery systems to provide a superior drug delivery system in terms of enhanced localization and drug targeting

Hazzah and *co-authors* [67] have successfully encapsulated curcumin into solid–lipid nanoparticles (CurSLN) based on Gelucire 50/13 and Poloxamer 407. The nano-system showed to be stable and maintained the stability of Curcumin against degradation in phosphate buffer /mucin in an attempt to mimic the salivary physiological condition. Moreover, CurSLN showed preferential mucosal uptake. The lipid nanoparticles were uniformly dispersed in a mucoadhesive gel matrix. Although *in vivo* residence time achieved was relatively of short duration (25 min), but it was quite enough to allow lipid nanoparticles penetration into the mucosal layer. Short-term clinical evaluation was carried out on 10 patients suffering oral erythroplakia in terms of pain index and lesion size measurement. The CurSLN-gel in a dose of (6mg/day) showed a pronounced effective pain index and reduction in the lesion size. Moreover, disappearance of the lesions, after 6-week course topical Curcumin treatment was observed. The authors also reported that clinical study on a long term and large number of participant enrolled should be carried out.

1.6. Curcumin and Mucositis

Patil *et al* [68] evaluated the efficacy and safety of curcumin mouthwash in reducing the severity of signs and symptoms of radio-chemotherapy induced oral mucositis in cancer patients. Curcumin mouthwash was well tolerated and effective in controlling the signs and symptoms of induced oral mucositis.

Elad *et al* [69], performed a pilot study on 7 paediatric patients receiving doxorubicin-containing chemotherapy. Chlorhexidine 0.2% mouthwash was used for 30 s twice per day compared to 10 drops of Curcumall twice per day in a mouthwash. In the four patients who fulfilled the compliance criteria, the WHO, OMAS and VAS scores were lower for Curcumin mouthwash compared to the scores of severity of oral mucositis previously reported in the literature.

Saldanha and Almeida [70] adopted two group pre-test post-test time series design to determine the effectiveness of Turmeric and Saline mouth wash on mucositis. Mouth wash was given three times daily for 5 days. The oral mucosa of the patients was assessed using an Oral Mucositis assessment checklist and pain using pain scale every morning before the intervention and evening after the intervention. The results revealed that there was a significant difference in the score of TIOM between pre-intervention on Day 1 morning and post intervention score on day 5 evening in turmeric and saline group. But on comparison it was found that turmeric mouth wash was effective than saline mouthwash in all the days except in Day 3 where there was no significant difference found. The authors concluded that both mouth washes were individually effective but on comparison turmeric mouth wash was better than saline.

III. CONCLUSION

As the number of research studies on the therapeutic effects of Curcumin keeps on increasing across the globe. It could be concluded that Curcumin holds a promising future in local therapeutic applications specific for oral diseases such as precancerous lesions and aphthous ulcers. This review highlighted–that curcumin is safe, non-toxic, effective and economical alternative with no side effects for many traditional drugs used in oral infection and periodontal diseases. Development of novel drug delivery systems such as nanoparticles and solid lipid nanoparticles loaded with curcumin seems to be very promising in enhancing its efficacy in addition to its stability and likely to be one of the thrust areas of research in future to optimize the use of this golden magical powder. Moreover, future research is required to determine the long-term effects of curcumin on a large number of subjects clinically.

REFERENCES

[1]. Gupta, S.C., Kim, J.H., Prasad, S., and Aggarwal, B.B., Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. *Cancer and Metastasis Reviews*, ***29 (****3)*, 2010, 405-434.

[2]. Bonifácio, B.V., Da Silva, P.B., Dos Santos Ramos, M.A., Negri, K.M.S., Bauab, T.M., and Chorilli, M., Nanotechnology-based drug delivery systems and herbal medicines: a review. *International Journal of Nanomedicine*, ***9*** 2014, 1.

[3]. Sankar, V., Hearnden, V., Hull, K., Juras, D.V., Greenberg, M., Kerr, A., Lockhart, P.B., Patton, L.L., Porter, S., and Thornhill, M., Local drug delivery for oral mucosal diseases: challenges and opportunities. *Oral Diseases*, ***17 (s1)***, 2011, 73-84.

[4]. Yakubov, G.E., Gibbins, H., Proctor, G.B., and Carpenter, G.H., *Mucoadhesive Materials and Drug Delivery Systems " Oral mucosa: physiological and physicochemical aspects"*. Vitaliy V. Khutoryanskiy ed. 2014, Chichester, West Sussex, UK: John Wiley & Sons. 35.

[5]. Munot, N.M. and Gujar, K.N., Orodental Delivery Systes: An Overview. *International Journal of Pharmacy & Pharmaceutical Sciences*, ***5 (3)***, 2013, 74-83.

[6]. Hearnden, V., Sankar, V., Hull, K., Juras, D.V., Greenberg, M., Kerr, A.R., Lockhart, P.B., Patton, L.L., Porter, S., and Thornhill, M.H., New developments and opportunities in oral mucosal drug delivery for local and systemic disease. *Advanced Drug Delivery Reviews*, ***64 (1)***, 2012, 16-28.

[7]. Nanci, A., *Ten Cate's Oral Histology-Pageburst on VitalSource: Development, Structure, and Function*. 7th ed. 2007: Elsevier Health Sciences 432.

[8]. Salamat-Miller, N., Chittchang, M., and Johnston, T.P., The use of mucoadhesive polymers in buccal drug delivery. *Advanced Drug Delivery Reviews*, ***57 (11)***, 2005, 1666-1691.

[9]. *The Human Protein Atlas :Dictionary : Normal Tissue, Oral Mucosa* in http://www.proteinatlas.org/learn/dictionary/normal/oral+mucosa, SciLifeLab.

[10]. Scholz, O.A., Wolff, A., Schumacher, A., Giannola, L.I., Campisi, G., Ciach, T., and Velten, T., Drug delivery from the oral cavity: focus on a novel mechatronic delivery device. *Drug Discovery Today*, ***13 (5)***, 2008, 247-253.

[11]. Sudhakar, Y., Kuotsu, K., and Bandyopadhyay, A., Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs. *Journal of Controlled Release*, ***114 (1)***, 2006, 15-40.

[12]. Maggi, L., Segale, L., Conti, S., Machiste, E.O., Salini, A., and Conte, U., Preparation and evaluation of release characteristics of 3TabGum, a novel chewing device. *European Journal of Pharmaceutical Sciences*, ***24 (5)***, 2005, 487-493.

[13]. Moyes, D.L. and Naglik, J.R., Mucosal immunity and Candida albicans infection. *Clinical and Developmental Immunology*, ***2011*** 2011,

[14]. Field, E., Brookes, V., and Tyldesley, W., R, Recurrent aphthous ulceration in children—a review. *International Journal of Paediatric Dentistry*, ***2 (1)***, 1992, 1-10.

[15]. Madrid, C., Jaques, B., Bouferrache, K., and Broome, M., How to cope with recurrent aphthous stomatitis. *Revue Medicale Suisse*, ***6 (265)***, 2010, 1871-1872, 1874-1877.

[16]. Akintoye, S.O. and Greenberg, M.S., Recurrent aphthous stomatitis. *Dental Clinics of North America*, ***49 (1)***, 2005, 31-47.

[17]. Pihlstrom, B.L., Michalowicz, B.S., and Johnson, N.W., Periodontal diseases. *The Lancet*, ***366 (9499)***, 2005, 1809-1820.

[18]. Medlicott, N.J., Rathbone, M.J., Tucker, I.G., and Holborow, D.W., Delivery systems for the administration of drugs to the periodontal pocket. *Advanced Drug Delivery Reviews*, ***13 (1)***, 1994, 181-203.

[19]. Albandar, J.M. and Rams, T.E., Global epidemiology of periodontal diseases: an overview. *Periodontology 2000*, ***29 (1)***, 2002, 7-10.

[20]. Yardimci, G., Kutlubay, Z., Engin, B., and Tuzun, Y., Precancerous lesions of oral mucosa. *World Journal of Clinical Cases: WJCC*, ***2 (12)***, 2014, 866.

[21]. Kumar, A., Cascarini, L., McCaul, J.A., Kerawala, C.J., Coombes, D., Godden, D., and Brennan, P.A., How should we manage oral leukoplakia? *British Journal of Oral and Maxillofacial Surgery*, ***51 (5)***, 2013, 377-383.

[22]. Warnakulasuriya, S., Johnson, N., and Van der Waal, I., Nomenclature and classification of potentially malignant disorders of the oral mucosa. *Journal of Oral Pathology & Medicine*, ***36 (10)***, 2007, 575-580.

[23]. Carnelio, S., Rodrigues, G.S., Shenoy, R., and Fernandes, D., A brief review of common oral premalignant lesions with emphasis on their management and cancer prevention. *Indian Journal of Surgery*, ***73 (4)***, 2011, 256-261.

[24]. Axell, T., Pindborg, J., Smith, C., and Waal, I.V., Oral white lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18–21 1994. *Journal of Oral Pathology & Medicine*, ***25 (2)***, 1996, 49-54.

[25]. Van der Waal, I., Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology*, ***45 (4)***, 2009, 317-323.

[26]. Haddad, R.I. and Shin, D.M., Recent advances in head and neck cancer. *New England Journal of Medicine, **359** (11),* 2008, 1143-1154.

[27]. Vogel, H. and Pelletier, J., Curcumin-biological and medicinal properties. *J. Pharma, **2*** 1815, 50.

[28]. Sharma, O., Antioxidant activity of curcumin and related compounds. *Biochemical Pharmacology, **25** (15),* 1976, 1811-1812.

[29]. Singh, S. and Aggarwal, B.B., Activation of transcription factor NF-κB is suppressed by curcumin (diferuloylmethane). *Journal of Biological Chemistry, **270** (42),* 1995, 24995-25000.

[30]. Negi, P., Jayaprakasha, G., Jagan Mohan Rao, L., and Sakariah, K., Antibacterial activity of turmeric oil: a byproduct from curcumin manufacture. *Journal of Agricultural and Food Chemistry, **47** (10),* 1999, 4297-4300.

[31]. Prasad, S., Tyagi, A.K., and Aggarwal, B.B., Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. *Cancer Research and Treatment: Official Journal of Korean Cancer Association, **46** (1),* 2014, 2.

[32]. Sharma, R., Gescher, A., and Steward, W., Curcumin: the story so far. *European Journal of Cancer, **41** (13),* 2005, 1955-1968.

[33]. Anand, P., Kunnumakkara, A.B., Newman, R.A., and Aggarwal, B.B., Bioavailability of curcumin: problems and promises. *Molecular Pharmaceutics, **4** (6),* 2007, 807-818.

[34]. Tønnesen, H.H., Solubility, chemical and photochemical stability of curcumin in surfactant solutions. Studies of curcumin and curcuminoids, XXVIII. *Die Pharmazie, **57** (12),* 2002, 820-824.

[35]. Tønnesen, H.H., Másson, M., and Loftsson, T., Studies of curcumin and curcuminoids. XXVII. Cyclodextrin complexation: solubility, chemical and photochemical stability. *International Journal of Pharmaceutics, **244** (1),* 2002, 127-135.

[36]. Tomren, M., Masson, M., Loftsson, T., and Tønnesen, H.H., Studies on curcumin and curcuminoids: XXXI. Symmetric and asymmetric curcuminoids: stability, activity and complexation with cyclodextrin. *International Journal of Pharmaceutics, **338** (1),* 2007, 27-34.

[37]. Kunnumakkara, A.B., Anand, P., and Aggarwal, B.B., Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Letters, **269** (2),* 2008, 199-225.

[38]. Mazzarino, L., Travelet, C., Ortega-Murillo, S., Otsuka, I., Pignot-Paintrand, I., Lemos-Senna, E., and Borsali, R., Elaboration of chitosan-coated nanoparticles loaded with curcumin for mucoadhesive applications. *Journal of Colloid and Interface Science, **370** (1),* 2012, 58-66.

[39]. Peng, S.-F., Lee, C.-Y., Hour, M.-J., Tsai, S.-C., Kuo, D.-H., Chen, F.-A., Shieh, P.-C., and Yang, J.-S., Curcumin-loaded nanoparticles enhance apoptotic cell death of U2OS human osteosarcoma cells through the Akt-Bad signaling pathway. *International Journal of Oncology, **44** (1),* 2014, 238-246.

[40]. Sun, J., Bi, C., Chan, H.M., Sun, S., Zhang, Q., and Zheng, Y., Curcumin-loaded solid lipid nanoparticles have prolonged in vitro antitumour activity, cellular uptake and improved in vivo bioavailability. *Colloids and Surfaces b: Biointerfaces, **111*** 2013, 367-375.

[41]. Manifar, S., Obwaller, A., Gharehgozloo, A., Boorboor Shirazi Kordi, H., and Akhondzadeh, S., Curcumin gel in the treatment of minor aphthous ulcer: A randomized, placebo-controlled trial. *Journal of Medicinal Plants, **1** (41),* 2012, 40-45.

[42]. Antharjanm, R. and Anita, B., Curcumin as a treatment modality in recurrent aphthous stomatitis. *Case Report. Kerala Dental Journal, **32** (4),* 2009, 206-208.

[43]. Nasra, M.M., Khiri, H.M., and Abdallah, O.Y., *Development of stabilized mucoadhesive tablets for buccal delivery of curcumin,* in *4th International Conference and Exhibition on Pharmaceutics & Novel Drug Delivery Systems*. 2014: San Antonio, USA.

[44]. Mali, A.M., Behal, R., and Gilda, S.S., Comparative evaluation of 0.1% turmeric mouthwash with 0.2% chlorhexidine gluconate in prevention of plaque and gingivitis: A clinical and microbiological study. *Journal of Indian Society of Periodontology, **16** (3),* 2012, 386.

[45]. Waghmare, P., Chaudhari, A., Karhadkar, V., and Jamkhande, A., Comparative Evaluation of Turmeric and ChlorhexidineGluconate Mouthwash in Prevention of Plaque Formationand Gingivitis: A Clinical and Microbiological Study. *The Journal of Contemporary Dental Practice, **12** (4),* 2011, 221-224.

[46]. Muglikar, S., Patil, K.C., Shivswami, S., and Hegde, R., Efficacy of curcumin in the treatment of chronic gingivitis: a pilot study. *Oral Health and Preventive Dentistry, **11** (1),* 2012, 81-86.

[47]. Behal, R., Mali, A.M., Gilda, S.S., and Paradkar, A.R., Evaluation of local drug-delivery system containing 2% whole turmeric gel used as an adjunct to scaling and root planing in chronic periodontitis: A clinical and microbiological study. *Journal of Indian Society of Periodontology, **15** (1),* 2011, 35.

[48]. Anuradha, B., Bai, Y.D., Sailaja, S., Sudhakar, J., Priyanka, M., and Deepika, V., Evaluation of Anti-Inflammatory Effects of Curcumin Gel as an Adjunct to Scaling and Root Planing: A Clinical Study. *Journal of International Oral Health: JIOH, **7** (7),* 2015, 90.

[49]. Merline, K.V., Nagarathma, D.V., and Litty, S., Curcumin and Metronidazole in Periodontal Therapy. *International Journal Research Ayunvenda Pharmaceutical* ***5(6)***, 2014, 380-384.
[50]. Suhag, A., Dixit, J., and Dhan, P., Role of curcumin as a subgingival irrigant: A pilot study. *Perio,* ***4 (2),*** 2007, 115-121.
[51]. Mazzarino, L., Borsali, R., and Lemos-Senna, E., Mucoadhesive Films Containing Chitosan-Coated Nanoparticles: A New Strategy for Buccal Curcumin Release. *Journal of Pharmaceutical Sciences,* ***103 (11),*** 2014, 3764-3771.
[52]. Gottumukkala, S.N., Sudarshan, S., and Mantena, S.R., Comparative evaluation of the efficacy of two controlled release devices: Chlorhexidine chips and indigenous curcumin based collagen as local drug delivery systems. *Contemporary Clinical Dentistry,* ***5 (2),*** 2014, 175.
[53]. Hazzah, H.A., Farid, R.M., Nasra, M., Hazzah, W.A., El-Massik, M.A., and Abdallah, O.Y., Gelucire-Based Nanoparticles for Curcumin Targeting to Oral Mucosa: Preparation, Characterization, and Antimicrobial Activity Assessment. *Journal of Pharmaceutical Sciences,* ***104 (11),*** 2015, 3913-3924.
[54]. Nandini, N., Vidya, D., and Komal, A., Comparative evaluation of 1% Curcumin solution and 0.2% Chlorhexidine irrigation as an adjunct to scaling and root planing in management of chronic periodontitis: A clinico-microbiological study. *Journal of Pharmaceutical and Biomedical Sciences (JPBMS),* ***14 (14),*** 2012,
[55]. Drake, D.R., Effects of environmental agents on bacteria from the oral cavity. 2004,
[56]. Gonzalez-Moles, M.A., Ruiz-Avila, I., Rodriguez-Archilla, A., Morales-Garcia, P., Mesa-Aguado, F., Bascones-Martinez, A., and Bravo, M., Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology,* ***95 (6)***, 2003, 688-692.
[57]. Paderni, C., Compilato, D., Giannola, L.I., and Campisi, G., Oral local drug delivery and new perspectives in oral drug formulation. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology,* ***114 (3),*** 2012, e25-e34.
[58]. Azuine, M.A. and Bhide, S.V., Chemopreventive effect of turmeric against stomach and skin tumors induced by chemical carcinogens in Swiss mice. *Nutrition and Cancer,* ***17 (1),*** 1992, 77-83.
[59]. Azuine, M., Kayal, J., and Bhide, S., Protective role of aqueous turmeric extract against mutagenicity of direct-acting carcinogens as well as benzo [a] pyrene-induced genotoxicity and carcinogenicity. *Journal of Cancer Research and Clinical Oncology,* ***118 (6),*** 1992, 447-452.
[60]. Das, A., Balan, A., and Sreelatha, K., Comparative Study of the Efficacy of Curcumin and Turmeric Oil as Chemopreventive Agents in Oral Submucous Fibrosis: A Clinical and Histopathological Evaluation. *Journal of Indian Academy of Oral Medicine & Radiology,* ***22 (2),*** 2010,
[61]. Solanki, S., Prasad, S., Chinmaya, B., Tandon, S., and Ashwini, B., The Magic of Herbal Curcumin Therapy in Recurrent Oral Lichen Planus. *American Journal of Ethnomedicine,* ***1 (1),*** 2014, 096-101.
[62]. Rai, B., Kaur, J., Jacobs, R., and Singh, J., Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. *Journal of Oral Science,* ***52 (2),*** 2010, 251-256.
[63]. Chainani-Wu, N., Madden, E., Lozada-Nur, F., and Silverman, S., High-dose curcuminoids are efficacious in the reduction in symptoms and signs of oral lichen planus. *Journal of the American Academy of Dermatology,* ***66 (5),*** 2012, 752-760.
[64]. Dudás, J., Fullár, A., Romani, A., Pritz, C., Kovalszky, I., Schartinger, V.H., Sprinzl, G.M., and Riechelmann, H., Curcumin targets fibroblast–tumor cell interactions in oral squamous cell carcinoma. *Experimental Cell Research,* ***319 (6),*** 2013, 800-809.
[65]. Kuttan, R., Sudheeran, P., and Josph, C., Turmeric and curcumin as topical agents in cancer therapy. *Tumori,* ***73 (1),*** 1987, 29-31.
[66]. Clark, C.A., McEachern, M.D., Shah, S.H., Rong, Y., Rong, X., Smelley, C.L., Caldito, G.C., Abreo, F.W., and Nathan, C., Curcumin inhibits carcinogen and nicotine-induced mammalian target of rapamycin pathway activation in head and neck squamous cell carcinoma. *Cancer Prevention Research,* ***3 (12),*** 2010, 1586-1595.
[67]. Hazzah, H.A., Farid, R.M., Nasra, M.M., Zakaria, M., Gawish, Y., El-Massik, M.A., and Abdallah, O.Y., A new approach for treatment of precancerous lesions with curcumin solid–lipid nanoparticle-loaded gels: in vitro and clinical evaluation. *Drug Delivery,* 2015, 1-11.
[68]. Patil, K., Guledgud, M.V., Kulkarni, P., Keshari, D., and Tayal, S., Use of Curcumin Mouthrinse in Radio-Chemotherapy Induced Oral Mucositis Patients: A Pilot Study. *Journal of Clinical and Diagnostic Research: JCDR,* ***9 (8),*** 2015, ZC59.
[69]. Meidan, I., Sellam, G., Simaan, S., Zeevi, I., Waldman, E., and Weintraub, M., Topical curcumin for the prevention of oral mucositis in pediatric patients: case series. *Alternative Therapies in Health and Medicine,* ***19 (3),*** 2013, 21.

[70]. Saldanha, S.P. and Almeida, V.D., A Comparative Study to Assess the Effectiveness of Turmeric Mouth Wash versus Saline Mouth Wash on Treatment Induced Oral Mucositis (Tiom) in a Selected Hospital at Mangalore. *Journal of Clinical Research & Bioethics,* ***5 (****6),* 2014, 1.