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Review

Therapeutic application of curcumin and its nanoformulation in dentistry: Opportunities and challenges

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Abstract: Curcumin (CUR) a natural polyphenolic compound, has attracted significant attention due to its broad-spectrum anti-inflammatory, antioxidant, antimicrobial, and antitumor activities. However, its poor water solubility, low bioavailability, and limited stability have hindered clinical applications. Novel approaches utilizing nanocarrier-based delivery systems (e.g., liposomes, micelles) and structural modification strategies offer promising solutions to enhance the therapeutic efficacy of curcumin. This review and analysis attempted to summarize the therapeutical applications and working mechanisms of CUR in oral infectious diseases, inflammation, traumatic disease and immune disorder. Publications included in this review included references were confined to curcumin, nano-curcumin (nCUR), and the names of different oral diseases; the different methodologies included clinical trials, in vivo animal studies and in vitro studies. Web of Science and Pubmed/MEDLINE databases were explored. The antioxidant, anti-inflammatory, immune regulation and anticancer properties of CUR and nCUR are reported, and their positive applications in oral diseases is discussed. With more favorable structure and improved solubility and bioavailability, nCUR is more beneficial, stable and efficient than CUR. Local application seems to be more effective on oral diseases, which allows for

higher concentrations and better bioavailability, and can directly targets specific areas of the mouth, providing more precise treatment. Both CUR and nCUR are likely to be developed into a next-generation drug, but there is no consensus on their concentration, irradiation times and light intensity. Additional trials are required to obtain clinical standards, and establish specific dose ranges and clinical procedures.

Keywords: curcumin; nanoformulation; oral diseases; clinical application; pharmacological mechanism

1. Introduction

Turmeric has been widely used as spice, dyes and medicinal agent. Its rhizome includes three main ingredients [1,2], among which curcumin (CUR) makes up approximately 60%–70% [3] (Figure 1A). CUR has low toxicity, excellent biological activity and antioxidative, anti-inflammatory, anticancer, anti-apoptosis and antibacterial effect. Researchers have evaluated its therapeutic effect on different systemic diseases [3–5]. CUR reduces the occurrence of atherosclerosis [6], prevents gastric mucosal damage [7] and has neuroprotective effects [8]. However, rapid elimination and low tissue accumulation are two main problems limiting its application [9].

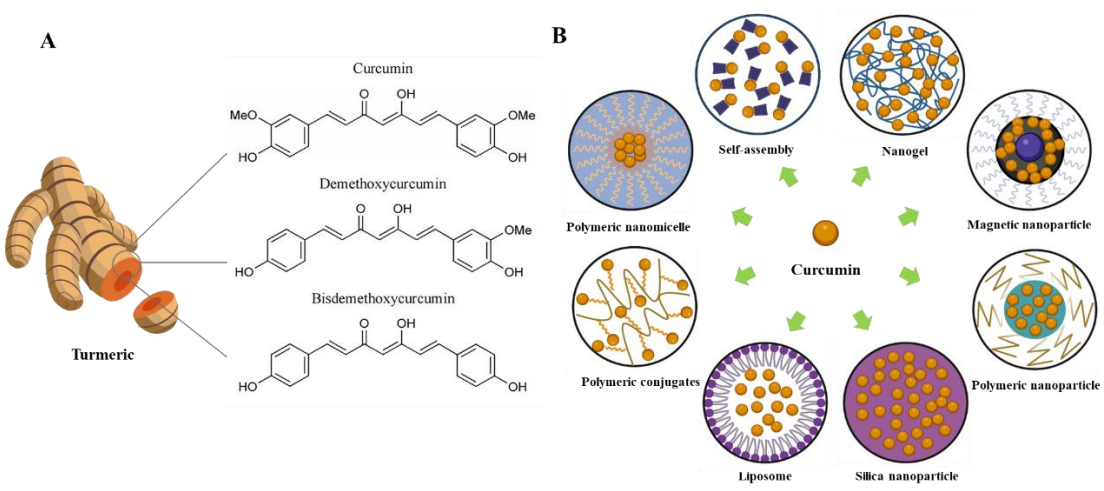

Figure 1. The chemical structure of turmeric (A) and different nanocarrier-based delivery systems of curcumin particles (B).

To address the shortcomings of native CUR, researchers have encapsulated CUR into nanocarrier-based delivery systems [10] (Figure 1B). The nanoformulations of CUR (nCUR) focus on improving solubility and bioavailability, protecting CUR from hydrolytic inactivation [11]. nCUR presents different particle size, surface area, charge and hydrophobicity than those of CUR, making it more effective in diagnosis [12] and pharmacological application [11].

Research has focused on potential for CUR and nCUR applications to systemic diseases, but its oral application remains unexplored. One study discussed CUR's use for oral mucosal disease, periodontal disease, and oral squamous cell carcinoma [13]; another focused on head and neck cancers

and salivary glands [11]. In this review, we included studied that focus specifically on the application of curcumin in oral diseases (e.g., anti-inflammatory, antibacterial, or anticancer effects); articles must be peer-reviewed English publications indexed in Web of Science or PubMed/MEDLINE (publication years: 2010–2025) and must contain in vitro, in vivo, or clinical research data.

2. Infection

CUR has been shown to have antibacterial properties against G^+ and G^- strains, including *Streptococcus mutans* (*S. mutans*) in caries and *Porphyromonas gingivalis* (*P. gingivalis)* in periodontal infection [14–16]. It exerts broad-spectrum antibacterial activity, including changing cell membrane permeability, weakening moving abilitys and changing virulence gene expression [14]. CUR causes oxidative stress and DNA damage, leading to the death and/or arrested growth of *Escherichia Coli* and *Staphylococcus aureus* [17]. nCUR has better antibacterial effect with improved solubility, bioavailability, and permeability [14].

Antibiotics are the primary therapy for bacterial infections. However, with the increase of drug resistance, CUR, with its non-selective acting mechanism, is an effective choice. CUR effectively kills methicillin-resistant *Staphylococcus aureus* [18], a drug-resistant pathogen causing nosocomial and community associated infections [19]. It also acts synergistically with antibiotics [20], facilitating their entrance into bacterial cells and even inhibiting cell division.

Antimicrobial photodynamic therapy (aPDT) is proven effective in reducing periodontal pathogens [21], *S. mutans* colonies, and *Staphylococcus aureus* strains [22] without affecting the quality of dental restoration [23]. When photosensitizer (PS) absorbs a specific wave length it undergoes electronic transition and energy transfer, causing reactive oxygen species (ROS) generation and oxidative damage to DNA, lipids, and proteins. G^+ bacteria are more sensitive to aPDT due to their cell wall structure [24]. CUR, as a PS, can activate aPDT [23] under the appropriate wave length (300–500 nm) [25,26], as shown in Figure 2. CUR-modified implants combined with aPDT inhibited *S. aureus* biofilms, reducing the occurrence of peri-implant infections [27]. CUR with aPDT has significant efficacy in reducing oral microbial load via mouthwash [28].

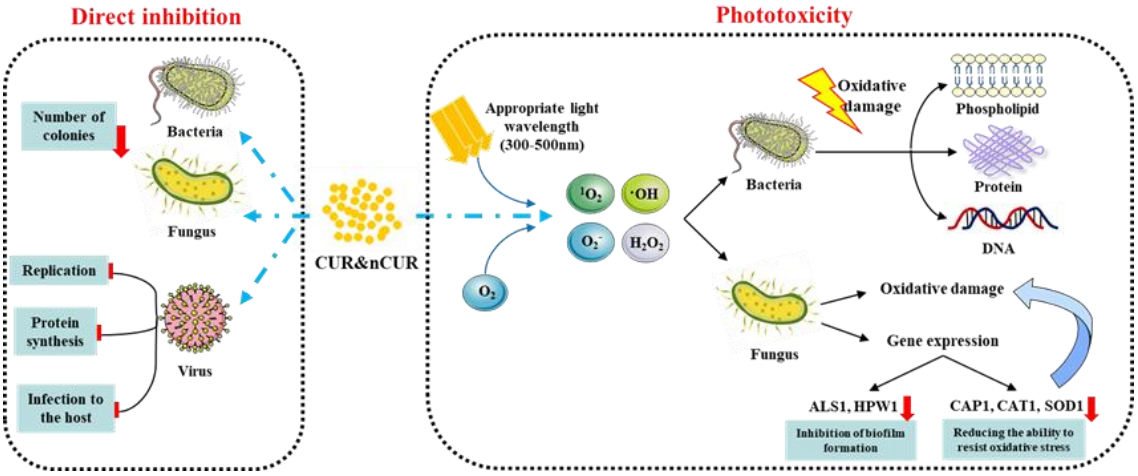

Figure 2. The mechanism of CUR and nCUR in treating microbial infections.

2.1. Dental caries

Dental caries is mainly caused by adhesion and colonization of *S. mutans*. CUR and nCUR inactivate *S. mutans* in planktonic suspension [29] and biofilm [30]; its anti-biofilm activity lasts from 5 min to 24 h, with a minimum concentration of 500 μM [31]. Biofilms are more resistant to aPDT [32]. An in vitro study tested the anti-biofilm effect of a pulp-capping agent with nCUR, where nCUR significantly decreased the number of *S. mutans* colonies in biofilm. This anti-biofilm property improves with concentration, and a pulp-capping agent with 5% (w/w) nCUR showed the best anti-biofilm ability up to 60 days [33]. However, tooth pigmentation will occur with high concentrations due to its yellow appearance. Using pre-irradiation (at least 2 min) to reduce the concentration and improve the efficiency of CUR has been proposed [34].

2.2. Pulp infection

E. faecalis is closely related to pulpal and periapical infection. Conventional methods utilizing sodium hypochlorite are not able to effectively kill *E. faecalis* in the root canal and may cause damage to periapical tissues [35,36]. CUR-aPDT represents an excellent alternative, effectively killing *E. faecalis* biofilm at concentrations as low as 10 μM [37], with a disinfection depth up to 400μm [38] and a reduction of the adverse effects of oxygen free radicals.

2.3. Peridontal and peri-implant infection

A. actinomycetemcomitans is one of the main pathogens responsible for aggressive periodontal infection. Limitations of mechanical removal of bacterial plaque are related to bacteria resistance and complex root anatomy. CUR-aPDT inhibits the growth and activity of *A. actinomycetemcomitans* and reduces the expression of biofilm-formation genes [39]. A clinical trial found that CUR-aPDT combined with scaling and root planning increased periodontal attachment [40]. Another study using 445 nm [40] and 660 nm [41] as excitation light showed antibacterial performance [42]. As for nCUR, a recent clinical trial using nCUR at 50 μg showed a reduction in "red complex species" count, and the amount of "beneficial bacteria" only increased in nCUR sites [43]. As for peri-implant infections, an in vitro study revealed that nCUR inhibited above 99% of peri-implant bacteria [44]. In addition to the direct inhibitory effect, CUR-aPDT can also indirectly act on untreated microbial cells whose population and metabolic activity were reduced [45]. Another study indicated that polydopamine-curcumin coating of titanium can remarkably inhibit bacterial activity via synergistic photodynamic and photothermal properties [46]. This provided a new foundation for the development of new Ti implants.

2.4. Fungal and viral infections

Oral candidiasis is one of the most opportunistic infections caused by *Candida yeasts*, mainly *C. albicans*. CUR-aPDT has shown inhibitory effects on *C. albicans* in planktonic and biofilm states, acting as a substitute for fluconazole [47]. An in vitro study showed that the expression of biofilm adhesion- and formation-related genes decreased with 80 μM CUR, and the ability to resist oxidative damage was reduced [48]. CUR-aPDT can reduce the load in biofilm composed of *S. mutans* and *C.*

albicans [49]. This antifungal action is similar to that of nystatin, indicating a new therapeutic modality for oral candidiasis to avoid nystatin toxicities [50].

CUR can inhibit virus replication and reduce virus entry pathway [51]. Herpes simplex virus-1 (HSV-1) is related to herpetic gingival stomatitis. CUR has shown therapeutic effects by inhibiting the replication and protein synthesis of HSV-1 [52] by transcription factor nuclear factor-κB (NF-κB) pathway and by inhibiting the activity of thymidine kinase [53]. Papillomaviruses belong to a group of tumor viruses associated with neck squamous cell carcinomas (HNSCC), which constitute about 4.5% of all solid tumors [54]. Curcumin liposomes were shown to be able to generate a PDT-triggered response in three papilloma virus-associated tumor cell lines, leading to major cell death [55].

The combination of nCUR with other drugs can enhance its anti-infectious properties especially for drug-resistant bacteria. In the future, new nanoformulations and combinations of CUR should be explored to improve its therapeutic potential, such as using nanotechnology targeting CUR to specific sites or using CUR as a carrier for other drugs.

3. Inflammatory diseases

CUR has anti-inflammatory effect and inhibits the expression of inflammation-related factors such as IL-6, IL-8, and TNF-α [56]. Researchers have summarized the anti-inflammatory mechanism of CUR, proposing that it inhibits inflammation by preventing formation of NOD-like receptor pyrin domain-containing 3 [57]. Given its anti-inflammatory effects, clinical trials have been carried out on pulp, periodontal, and peri-implant inflammation.

3.1. Pulp inflammation

2-Hydroxyethyl methacrylate is commonly used in tooth restoration. However, it increases inflammation in pulp stem cells and causes inflammatory response. CUR-encapsulated liposome inhibits pathway signaling molecules such as NF-κB, ERK, and pERK to reduce inflammatory side effects [58]. The next step is to restore tooth anatomy and function. Stable bond between dentin and resin adhesive is the key to successful restoration. However, matrix metalloproteinases and cathepsin K will cause collagen degradation in the hybrid layer [59,60], not conducive to dentin and adhesive connection. CUR has shown long-term effect on inactivating these endogenous proteases, with 200 μM CUR leading to irreversible inactivation of cathepsin K over a 6-month period [61–63], so that a successful tooth restoration can be guaranteed.

3.2. Periodontital inflammation

Periodontal inflammation is characterized by progressive gingival inflammation and irreversible alveolar bone loss. Stimulated by lipopolysaccharides (LPS), the NF-κB signaling pathway can be activated and inflammatory cytokines like IL-1β and TNF-α are produced, causing progressive destruction. CUR reduces periodontal inflammation by inhibiting TNF-α and IL-1β [64] and reduces damage to periodontal tissue [65]. Osteoprotegerin (OPG) and soluble receptor activator of nuclear factor kappa-B ligand (RANKL) are essential for alveolar bone metabolism. CUR attenuates LPS-induced osteoclast activation and inhibits alveolar bone resorption by down regulating OPG/sRANKL ratio, as proved in an in vivo study [64]. It also reduces MMP-9 expression to regulate extracellular

matrix degradation and remodeling [66]. As for clinical treatment of periodontitis, 1% CUR gel offered equivalent benefits in reducing pocket depth after scaling and root planning [67]. Mouthwashes containing CUR can treat gingivitis by exerting anti-plaque and anti-inflammatory effects [68]. As for nCUR, a recent clinical trial using nCUR soft gel capsules locally found it effective on inflammation in patients with gingivitis and mild periodontitis, with severe decreases in papillary bleeding index (PBI) and modified gingival index (MGI) [69]. Due to better biological effectiveness and few side effects, nCUR can be used as a complementary therapy.

3.3. Oral mucosal inflammation

Oral submucous fibrosis (OSMF) is a chronic inflammatory disease invading oral mucosa, which causes trismus, interferes with normal functions, and leads to malignant transformation [70,71]. Chronic and progressive submucosal fibrosis is a common clinical manifestation, causing decreased blood vessels and tissue ischemia [72]. Curcumin reduces the transcription level of LTBP2 by inhibiting HIF-1α, thereby inactivating the NF-κB pathway to alleviate arecoline-induced OSMF [73]. Different treating methods are used clinically, mainly focusing on palliative care rather than complete cure. Some clinical studies showed that CUR has anti-inflammatory and anti-oxidation effects, effectively reducing burning sensation and increasing mouth opening [71,74,75]. This is due to CUR's ability to reduce expression of pro-inflammatory cytokines and remove ROS [76]. Protein of p53, TGF-β and iNOS are down-regulated with CUR intake, showing the chemopreventive property of CUR in OSMF management [77]. Further clinical confirmations are still needed to evaluate CUR's potential in the treatment of OSMF [13,78,79].

Recurrent aphthous stomatitis (RAS) is a prevalent inflammatory condition appearing as multiple, small, cupped, round, or oval-shaped symmetrical lesions of oral mucosa. After topical application of both 1% nCUR gel and 2% CUR gel for 7 days, pain score and lesion size were significantly decreased [80]. Greater reductions of the above indexes were discovered in the nanomicelle group, showing that nCUR was more effective than CUR and contributed to its better substantivity, solubility, and bioavailability.

3.4. Inflammation after implantion

Success of oral implantation depends on good osseointegration between the implant and surrounding bone tissues. However, foreign body reactions induced by implant placement may result in significant inflammation, which in turn affects wound healing and osseointegration and will cause implant failure [81]. Investigations performed in vivo with animal models revealed that CUR inhibits activation of Akt/NF-κB/NFATc1 pathways and production of CCL3, thus reducing bone mass loss [82,83]. Besides, CUR can regulate osteoblastic, osteoclastic, and adipogenic differentiation of mesenchymal stem cells (MSCs) [84]. It promotes osteoblastic differentiation of MSCs; the signaling pathways of ER stress, Wnt/β-catenin, Akt/GSK3β, and Keap1/Nrf2/HO-1 have been identified as the potential mechanisms. CUR has stronger inhibitory effect against osteoclastic differentiation via inhibition of RANKL/RANK and NF-κB as well as activation of Wnt/β-catenin pathways. Also, it suppresses MSCs from adipogenic differentiation via AMPK regulation and activation of Wnt signaling pathway. Furthermore, it attenuates the up-regulation of Akt/NF-κB pathways, PPARγ signaling pathway [85], and p65 phosphorylation and promotes the polarity of macrophages from M1 phenotype to M2 phenotype. Expressions of IL-4, IL-10, and CD206 are increased and those of IL-1β,

TNF-α, CCR7, and iNOS are decreased, contributing to improved osteogenic microenvironment [83,85,86]. Recent in vivo researches applying CUR onto Mg or TiO_2 implant surfaces [26,86,87] showed that osteogenesis was promoted and local inflammation was reduced around implant post-modification. Surface modification of implants with CUR can help promote osseointegration as well as control local inflammation so as to achieve the success of oral implantation.

3.5. Temporomandibular arthritis

CUR can protect temporomandibular cartilage from degradation by inhibiting the expression of various inflammatory factors. Reviews show that it inhibits the expression of ROS and MMPs induced by IL-1β [88]. Additionally, it increases the expression of the anti-inflammatory factor Nrf2, up regulates cartilage synthesis factor COL2A1 and ACAN, and activates ROS/Nrf2/HO-1-SOD2-NQO-1-GCLC signaling axis, which plays an important role in anti-inflammatory and cartilage protective effects [88]. This information provides new ideas for the treatment of temporomandibular arthritis, although more clinical trials are needed.

4. Traumatic diseases

Oral and maxillofacial injuries include soft tissue damage, bone fractures, and teeth and alveolar processes [89], such as teeth dislocation and fracture, maxilla or mandible injury and traumatic joint injury [90,91]. Wound healing can be divided into four stages: coagulation, inflammation, migration-proliferation, and remodeling [92,93], also applicable in oral trauma diseases. There are known mechanisms of CUR during certain stages of healing for systemic diseases [94], and this section elaborates the role of CUR in all stages for oral trauma.

In the coagulation stage, clotting and hemostasis start immediately. The coagulation pathway is activated, causing platelet aggregation. While the hemostatic pathway is ongoing, reactive vasoconstriction decreases, or even stops, bleeding [95]. CUR can be widely used in thromboembolism because it can inhibit platelet aggregation, anticoagulation, and fibrinolysis [96,97]. The pharmacological effects of CUR are the same in the coagulation phase of oral trauma.

During the inflammatory period, inflammatory factors are upregulated with the activation of NF-κB. These inflammatory factors attract more inflammatory cells, induce production of ROS, and cause further injury [98]. As widely reported, CUR reduces expression of pro-inflammatory cytokines and controls the activity of kinases to reduce inflammation [94], as shown in Figure 3. CUR also has antioxidant effects by scavenging ROS and inhibiting transcription factors related to oxidation [99,100]. In a palatal rat model, topical application of 2% CUR pastes reduced the infiltration rate of inflammation [101], while in another study, tissue edema was reduced and tissue color was normalized following periodontal flap surgery using CUR. CUR allows later stages of healing to begin earlier by limiting the former inflammation [102].

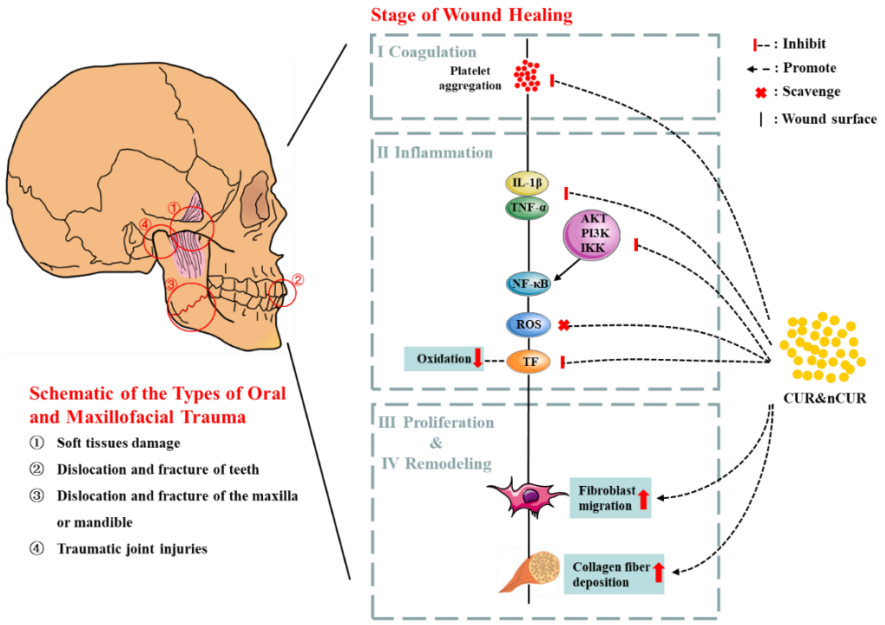

Figure 3. Types of oral trauma and effects of CUR and nCUR on wound healing in different stages (IL-1β: interleukin-1β; TNF-α: tumor necrosis factor; NF-κB: nuclear factor kappa-B; ROS: reactive oxygen species; TF: transcription factors related to oxidation; AKT, PI3K, IKK: activity of kinase).

During proliferation and remodeling phases, CUR accelerates wound healing by enhancing fibroblast proliferation and epithelialization, accelerating granulation tissue formation, promoting collagen fiber deposition, and increasing wound contraction [103–105]. A study showed that CUR promoted epithelization of oral mucosa epithelial cells in rat primary palatal wounds [100]. Another showed that topical use of 25% CUR ointment on gingival healing in dogs normalized the degree of re-epithelialization, and collagenous fibers were arranged in a compact and orderly manner [106]. CUR strengthens wound closure by upregulating fibroblast growth into trauma, promoting earlier re-epithelialization, improving neovascularization, and increasing collagen content [105,106]. Moreover, using CUR after tooth extraction can stimulate fibroblast and collagen fibers proliferations to promote tissue regeneration [107,108]. A special mechanism of CUR was found in oral wound healing, with a recent study reporting that CUR significantly upregulates expression of collagen type I, keratinocyte growth factor-1, and epidermal growth factor receptor, playing a key role to promote wound healing, in the wound-healing and unwound-healing modes of human gingival fibroblasts [109].

5. Immune disorders

Immune disorders take many forms in oral cavity, including oral carcinoma and mucosal lesions such as geographic tongue, oral lichen planus, and mucositis [110]. CUR and nCUR regulate immune cell function, are synergistic with antioxidants, and have anticarcinogenic and anti-inflammatory properties, which make them appropriate to exert therapeutic action in oral immune disorders.

5.1. Oral squamous cell carcinoma

CUR has reliable anti-cancer effects whose mechanisms include inhibiting cancer cell proliferation, promoting apoptosis, regulating miRNA, and epithelial-mesenchymal transition [111,112]. Squamous cell carcinoma of the head and neck (HNSCC) is considered the sixth most common cancer, which appears in gums, mucosa, lips, tongue, and hard palate and accounts accounting for approximately 90% of oral cancers [113]. Tongue cancer is the most common, making up approximately half of all incidences, presenting a very rich blood supply and a high rate of lymphatic metastasis, thus resulting in a poor prognosis.

Clinical usage of CUR and nCUR in preventing and treating HNSCC include marked decrease of oral carcinoma formation in hamster buccal pouch model of carcinogenesis and decrease of proinflammatory cytokine and IκB kinase-β activity in saliva [11]. The increased permeability and retention of nCUR improve local accumulation, enhance cellular transport process and thus improve extracellular level, appearing to be excellent in vivo. As for the mechanism (Figure 4), CUR increases the cellular ratio of Bax/Bcl-2 in tongue squamous cell carcinoma and increases cleaved Caspase-3 content, causing apoptosis [114,115]. It increases the number of cells staying in S or G2/M phase and inhibits tumor cell proliferation [115–117]. CUR inhibits immune tolerance, by the inhibition of signal transducer and activator of transcription 3 (STAT3) phosphorylation and PD-L1 expression [116–119]. CUR reduces the number of immunosuppressive cells induced by 4-nitroquinoline-oxide and effectively reduced tumor volume [117]. As for tumor metastasis, CUR inhibits HGF-induces HSC-4 and Ca9-22 epithelial-mesenchymal transition by inhibiting c-Met and ERK phosphorylation [120]. CUR can inhibit angiogenesis, with researchers believing that CUR's anti-cancer effect is related to its enhancement of SIRT1 deacetylation activity [121].

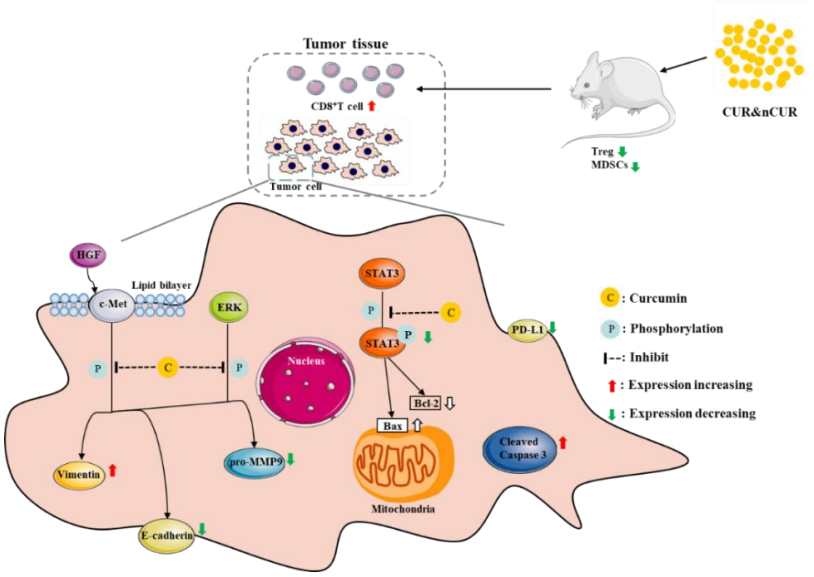

Figure 4. The potential mechanism of CUR and nCUR against oral squamous cell carcinoma (MDSCs: myeloid-derived suppressor cells; HGF: hematopoietic growth factor; c-Met: cellular-mesenchymal epithelial transition factor; ERK: extracellular regulated protein kinases; E-cadherin: epithelial cadherin; STAT3: signal transducer and activator of transcription 3; PD-L1: programmed death-ligand).

Chemotherapy and radiotherapy are commonly utilized in oral carcinoma, but with side effects like toxicity to normal cells and resistance of tumor cells. CUR combined with chemotherapy enhances therapeutic effect. In vitro and in vivo studies proved that nCUR combined with 5-fluorouracil can promote cell apoptosis, and CUR hindered DNA repair combined with Olaparib [122–124]. CUR also has protective effect during chemotherapy, reduces side effects and prolongs application time [125]. Radiotherapy can cause oxidation and change crystal structure of enamel, which can be prevented by CUR via resisting oxidative stress [126,127]. Orally taking nCUR helps to reduce the incidence and severity of radiotherapy-induced mucositis [128], which can be a reasonable approach to hinder oral mucositis in HNSCC patients requiring radiotherapy.

5.2. Psoriasis and geographic tongue

Psoriasis is an autoimmune disease presenting as characteristic skin [129] and oral lesions [130]. The pathological changes are primarily shown as geography tongue, which is believed to be related to the severity of psoriasis [131,132]. The production of inflammatory infiltration in psoriatic lesions were mediated by immune cells, especially T cells. Those inflammatory factors include IL-17, IL-22, IFN-γ, IL-2, IL-8, and TNF-α [133,134]. CUR has anti-inflammatory properties [135]. An animal experiment indicated that CUR inhibits proliferation of T cells and secretion of inflammatory factors [136]. More trials are needed to confirm its clinical effect.

5.3. Oral lichen planus

Oral lichen planus (OLP) is a kind of oral mucosal disease with chronic inflammation and erosion [137], which is mediated by T cells and pro-inflammatory mediators released by mast cell degranulation [138,139]. Topical corticosteroids are commonly used clinically, with many side effects [140]. With strong anti-inflammatory properties and fewer side effects [141], clinical studies have explored the use of CUR in OLP to reduce pain and burning sensation. There are statistically significant differences in pain severity and clinical manifestations after topical treatment with nCUR (as low as 10mg once daily), but no statistically significant differences with respect to its efficacy versus corticosteroids [142–144]. Due to CUR's treatment efficiency and fewer side effects, it can be used as an adjuvant in combination with corticosteroids.

6. Preparation and production cost of curcumin and its nanoformulation

As a natural polyphenol compound, curcumin has attracted much attention because of its anti-inflammatory, antioxidant, and anticancer activities, but its clinical application is limited by problems such as poor water solubility, low bioavailability, and insufficient chemical stability. Nanoformulation technology significantly improves the therapeutic effect of curcumin by improving its physicochemical properties. The following will compare curcumin and its nanoformulation in terms of preparation process, carrier selection, and production cost, and compare the cost-effectiveness of liposomes, PLGA polymers, and natural polymer carriers.

6.1. Comparison of curcumin and its nanoformulation

Due to its poor water solubility, low intestinal absorption rate, and fast metabolism, curcumin requires high doses or frequent administration to achieve curative effects, which increases patients' medication costs and potential risk of side effects [144]. Nanoformulations can improve solubility and stability, prolong blood circulation time, and achieve targeted delivery by carrier encapsulation or composite technology. For example, chitosan nanocomplexes are combined with curcumin by electrostatic interaction with up to 60% drug loading without complex encapsulation processes, significantly reducing costs [145]. Furthermore, nanoformulations can enhance tumor targeting through surface modification and reduce systemic toxicity [146].

6.2. Limitations of liposomes and PLGA polymer carriers

As classical nanocarriers, liposomes have the advantages of high biocompatibility and stable encapsulation efficiency, but their preparation requires phospholipid materials and precise processes, such as film hydration method, resulting in high production costs [146]. In addition, liposomes are prone to oxidative degradation and require low-temperature storage, further increasing the cost of cold chain transportation. PLGA (polylactic acid-glycolic acid copolymer) is an FDA-approved synthetic polymer with controlled release characteristics, but its synthesis relies on petroleum-based raw materials and the cost is high. The preparation of PLGA nanoparticles often requires the use of organic solvents, such as dichloromethane, which poses environmental and safety risks, and the cumbersome later purification steps increase the preparation cost [147]. In clinical transformation, the large-scale production cost of PLGA has become the main bottleneck.

6.3. Cost advantages and innovative applications of natural polymer carriers

Compared with synthetic materials such as liposomes or PLGA, natural polymers, such as chitosan and gelatin, have become the preferred nano formulations because of their wide range of sources, good biodegradability and low cost. The amorphous curcumin-chitosan nanocomposite developed by Nguyen et al. (2015) was prepared by a simple ionic gelation method, avoiding the use of organic solvents [145]. The drug loading capacity was more than 3 times that of traditional nanoparticles, and the supersaturated solubility was high, significantly improving bioavailability. The process saves the packaging step, reduces the production costs by more than 50%, and is suitable for industrial production.

6.4. Comprehensive analysis of production cost

The cost of nano formulation mainly includes three parts: materials, processes and large-scale production. Liposomes and PLGA rely on high-purity synthetic materials, accounting for 40%–60% of the cost [146]; However, the price of natural polymer raw materials such as chitosan is only 1/5-1/10 of that of synthetic materials [145]. In terms of technology, natural carriers mostly adopt mild conditions,such as aqueous phase reaction, and energy consumption and equipment investment are low. For example, curcumin-chitosan complexes can be prepared only by stirring and centrifugation, while liposomes require complex steps such as high-pressure homogenization [147]. In large-scale

production, natural polymers are easier to achieve continuous production, which is in line with the trend of "green chemistry".

While improving the curative effect, nano-curcumin needs to take into account the preparation economy. Although the performance of liposomes and PLGA is controllable, the cost and process limit their popularity. Natural polymer carriers have become a more competitive choice by simplifying processes and reducing raw material costs. Future research should further optimize the stability and targeted modification of natural materials to promote the transformation of nano-curcumin from laboratory to clinic.

6.5. Therapeutic efficiency and long-term economics of curcumin and its nanoformulations

Curcumin has attracted much attention due to its anti-inflammatory, antioxidant, and anticancer properties, but its clinical application has long been limited by low bioavailability (<1%) and frequent administration requirements. By improving the solubility, targeting and stability of curcumin, nano-formulation technology significantly improves the treatment efficiency and reduces the economic burden of long-term medication. The following will be analyzed from the aspects of bioavailability improvement, medication frequency optimization, nursing cost reduction and side effect management cost reduction.

Nano-curcumin can break through the biological barrier and greatly improve the drug absorption efficiency through carrier wrapping or structural modification. Szymusiak et al. (2016) found that the concentration of curcumin and its active metabolite (curcumin glucuronide) in the central nervous system of mice orally administered nano-curcumin (particle size < 100 nm) was 5-8 times higher than that of the traditional curcumin group, indicating that nano-curcumin significantly enhances blood-brain barrier penetration ability [148]. The improvement of the bioavailability of nano-curcumin directly reduces the dosage and frequency of administration, and the high curative effect reduces the frequency of hospitalization or follow-up visits, reduces nursing costs and the burden on patients, and indirectly saves medical resources. For example, in the treatment of recurrent aphthous ulcer (RAS), the clinical trial of Bakhshi et al. (2022) showed that the efficacy of 1% nano-curcumin gel (drug loading optimization) was comparable to that of 2% traditional curcumin gel, but the number of daily doses was reduced from 4 to 2, and patient compliance was significantly improved. The healing time of nano-curcumin gel was shortened by 30% compared with traditional preparations, the patient care cycle was reduced from an average of 14 days to 10 days, the number of outpatient follow-up visits was reduced, and the comprehensive care cost was reduced by about 25% [149]. Through targeted delivery and sustained release properties, nanoformulations can accurately act on the lesion area, shorten the course of treatment and reduce the intensity of care. Hafez Ghoran et al. (2022) pointed out that curcumin nanoparticles (such as liposomes, micelles) can achieve pH-responsive release in the tumor microenvironment, and the anti-cancer efficiency is 3-5 times higher than that of free curcumin [150].

Traditional curcumin requires high-dose administration (usually > 8 g/day) and easily causes gastrointestinal reactions such as diarrhea and nausea, while nano-formulations significantly improve safety and reduce side effect management costs by reducing effective doses and systemic exposure. Szymusiak et al. (2016) confirmed that nano curcumin did not cause elevated liver enzymes or histopathological damage in mouse models, and its safety profile was better than free curcumin [148]. The clinical trial of Bakhshi et al. (2022) further showed that the incidence of adverse reactions in the

1% nanogel group (8%) was significantly lower than that in the 2% traditional gel group (24%), and the cost of additional medical interventions (such as anti-nausea drugs and electrolyte supplementation) due to side effects was reduced by about 40% [149].

Nano curcumin achieves reduction and efficiency increase by improving bioavailability, optimizing targeting, and reducing toxic and side effects, thereby reducing drug frequency, nursing investment, and side effect management costs. In the long run, although the early research and development cost of nanoformulations is high, their comprehensive economics (such as shortening the course of treatment and saving medical resources) increase their potential for application in the treatment of chronic diseases and cancer. In the future, it is necessary to further optimize large-scale production processes to reduce production costs and promote clinical popularization.

6.6. Economic analysis of curcumin and its nanoformulations in global healthcare systems

As a natural polyphenol compound, curcumin has a wide range of pharmacological abilities in anti-inflammatory, antioxidant and anticancer fields, but its clinical application is limited by low water solubility, rapid metabolism and low bioavailability. Nano-formulation technology has significantly improved the efficacy of curcumin by improving its physical and chemical properties, but its economy and accessibility are significantly different between developed and developing countries.

6.7. The technical cost of nano-formulations and the application advantages in developed countries

In developed countries, the preparation of nano-curcumin mostly adopts high-precision technologies, such as liposome encapsulation, polymer nanoparticles (PLGA) and micellar systems. Although these technologies have high preliminary R&D and equipment investment costs (such as high-pressure homogenization, supercritical CO_2 extraction, etc.), they can achieve large-scale production, thus diluting the cost of a single agent [151]. In addition, the perfect medical insurance system and high patient payment ability in developed countries have further improved the accessibility of nano-formulations.

6.8. Cost challenges and potential opportunities for developing countries

Developing countries are limited by technology and funds, and often use natural polymers (such as chitosan and zein) or simple nano-preparation processes (such as ionic gel method and solvent evaporation method) to reduce production costs. However, technology reliance on imported equipment (such as nanoflow cytometry, high performance liquid chromatography) and patent licensing fees still push up terminal prices.

Developed countries can rapidly promote the clinical application of nano-curcumin by virtue of their technological advantages and high payment ability. Developing countries need to gradually break through technical and economic barriers by combining raw material advantages with low-cost processes. In the future, technology transfer, promotion of green preparation processes (such as plant-derived nanocarriers), and international collaboration are expected to narrow the gap between the two and promote the inclusive application of nano-curcumin in the global medical system.

7. Limitations

Although CUR and nCUR has been proved effective on all kinds of oral diseases, there is no consensus on CUR's concentration, irradiation time, and light intensity. High CUR concentration or excessive light intensity can reduce the activity of mice fibroblasts. CUR of different concentrations (0.01, 0.1, 1, 10, 100μM) changes activity of human gingival epithelial precursor cells, which decrease significantly at more than 10 μM [66]. It may promote apoptosis in fibroblasts, although tangible evidence is still lacking [34]. As for the effect on oral stem cells, one study pointed out that high doses of CUR (>10 μM) can overexpress miR-126a-3p in human bone marrow mesenchymal stem cells, which inhibits osteogenic differentiation, reduces bone mass and increases risk of tumor metastasis [152]. Besides, CUR promotes apoptosis and migration, resulting in adverse effects [153]. Higher concentration or two photodynamic therapy sessions may cause adhesive failure, since the high CUR concentration or hydrogen peroxide formed during the photodynamic therapy session may react with calcium ions in hydroxyapatite. [154–156].

CUR and nCUR have a promising future in the treatment of oral diseases. Existing studies have reported that topical application of about 1% to 2% concentrations of CUR can play an effective therapeutic role. Research is still necessary to further explore the dose-concentration relationship and achieve the most beneficial efficiency. While this study centers on mechanistic investigations, critical evaluation of the cited studies could provide additional translational value, particularly in oral applications where clinical evidence remains sparse.

8. Conclusions

This review highlights the therapeutic potential of CUR in oral diseases and the advantages of nCUR in pharmacological effectiveness and clinical application. We briefly illustrate mechanisms of CUR by inhibiting various proteins and signaling pathways associated with development and progression of oral diseases. The antioxidant, anti-inflammatory, immune regulating, anticancer properties of CUR and nCUR are reported, suggesting that they may have positive applications to oral diseases. CUR has certain shortcomings including low solubility and poor bioavailability, but nCUR, with more favorable structure, is more beneficial and stable [14]. Local application is shown to be more effective for oral diseases, which directly targets specific areas, provides more precise treatment, and allows for higher concentration and better bioavailability.

The therapeutic application of CUR and nCUR should be considered in oral diseases including oral infection, inflammation, traumatic disease, and immune disorder. Still, additional systematic trials are required, as the existing evidence is not sufficient for clinical standard, and the specific dose and clinical procedure need to be established. In the future, it is necessary to further study the optimal concentration range of nanocurcumin in different diseases, and how to further improve its distribution and targeting in vivo by optimizing the design and preparation process of nanocarriers. Furthermore, more preclinical and clinical studies are needed to determine the optimal irradiation time of curcumin and nano formulations in different cancer types and treatment regimens, and how to optimize their combined application with radiotherapy. Further research on the photochemical reaction mechanism of curcumin under different light intensities and how to improve its stability and bioavailability by optimizing light treatment conditions is needed.

Author contributions

QL and JMX designed the study; JZ and LH performed data collection and literature analysis; JMX prepared figures and tables; YP and SH prepared initial draft; ZJ, CY and SZ contributed to review and editing. All authors approved the final version of the manuscript.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest.

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