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**Therapeutic potential of curcumin and its nanoformulations for treating oral cancer**

Mukherjee D *et al*. Curcumin’s recent advances in oral cancer

Diptasree Mukherjee, Arunkumar Krishnan

**Diptasree Mukherjee,** Department of Biochemistry, All India Institute of Medical Sciences, Bhubaneswar 751019, Odisha, India

**Diptasree Mukherjee,** Department of Medicine, Apex Institute of Medical Science, Kolkata 700075, West Bengal, India

**Arunkumar Krishnan,** Department of Medicine Section of Gastroenterology and Hepatology, West Virginia University School of Medicine, Morgantown, WV 26505, United States

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**Corresponding author: Arunkumar Krishnan, MBBS, Doctor,** Department of Medicine Section of Gastroenterology and Hepatology, West Virginia University School of Medicine, PO Box 9161, 5th Floor HSC, Room 5500 Morgantown, WV 26505, United States. dr.arunkumar.krishnan@gmail.com

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**Abstract**

The global incidence of oral cancer has steadily increased in recent years and is associated with high morbidity and mortality. Oral cancer is the most common cancer in the head and neck region, and is predominantly of epithelial origin (*i.e.* squamous cell carcinoma). Oral cancer treatment modalities mainly include surgery with or without radiotherapy and chemotherapy. Though proven effective, chemotherapy has significant adverse effects with possibilities of tumor resistance to anticancer drugs and recurrence. Thus, there is an imperative need to identify suitable anticancer therapies that are highly precise with minimal side effects and to make oral cancer treatment effective and safer. Among the available adjuvant therapies is curcumin, a plant polyphenol isolated from the rhizome of the turmeric plant *Curcuma longa*. Curcumin has been demonstrated to have anti-infectious, antioxidant, anti-inflammatory, and anticarcinogenic properties. Curcumin has poor bioavailability, which has been overcome by its various analogues and nanoformulations, such as nanoparticles, liposome complexes, micelles, and phospholipid complexes. Studies have shown that the anticancer effects of curcumin are mediated by its action on multiple molecular targets, including activator protein 1, protein kinase B (Akt), nuclear factor κ-light-chain-enhancer of activated B cells, mitogen-activated protein kinase, epidermal growth factor receptor (EGFR) expression, and EGFR downstream signaling pathways. These targets play important roles in oral cancer pathogenesis, thereby making curcumin a promising adjuvant treatment modality. This review aims to summarize the different novel formulations of curcumin and their role in the treatment of oral cancer.

**Key Words:** Oral cancer; Oral squamous cell carcinoma; Analogues; Curcumin; Adjuvant therapy; Nanocurcumin; Curcumin nanoformulations; Curcumin analogues

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**Core Tip:** Oral cancer has a high disease burden worldwide. Oral squamous cell carcinoma is the most predominant subtype of oral cancer. The majority of oral cancers present at an advanced stage and are associated with a poor prognosis. Timely diagnosis and early treatment are critical to achieve a superior outcome. Surgery is the recommended treatment for oral cancer; other treatment modalities are radiotherapy with or without chemotherapy. Curcumin, a plant derivative, is one among the available adjuvant therapies that has been studied for its anticarcinogenic potential in the setting of various cancers. Curcumin has been proven to modulate intracellular signaling pathways that control cancer cell growth, inflammation, invasion, apoptosis, and cell death, with evidence supporting its use in cancer therapy. This review aims to summarize the molecular pathways involved in oral carcinoma pathogenesis, to explore different therapeutic interactions of curcumin, and to highlight the role of novel curcumin formulations in oral cancer treatment.

**INTRODUCTION**

Oral cancer, a disease of predominant epithelial origin, is the most common subtype of cancer arising in the head and neck[1]. In 2020, more than 300000 new oral cancer cases were recorded globally[2]. Ninety percent of oral cancer cases are histologically diagnosed as oral squamous cell carcinomas (OSCCs)[3]. Oral cancer is widely prevalent in developing countries of South Central Asia (*e.g.,* India, Sri Lanka, Pakistan) and Melanesia, with a lesser disease burden in developed countries[4]. Oral cancer is the leading cause of death due to cancer in the Indian male population[5]. High incidence rates of oral cancer have been linked to alcohol consumption, tobacco smoking, betel nut chewing, and human papillomavirus (HPV) infection[6]. Despite diagnostic and therapeutic advances, the global 5-year survival rate remains less than 50%[7].

The primary treatment of oral cancer is based on the cancer stage. Surgery is the mainstay of multimodal therapy, which also includes radiotherapy and systemic treatment (chemotherapy and/or targeted agents)[8]. Chemotherapy has proven to increase treatment efficacy and improve overall survival, but has significant adverse effects and the potential for development of drug resistance[9]. As such, combination of these therapies with an adjuvant treatment to bolster their efficacy is urgently needed.

Among adjuvant therapies is curcumin, a phytochemical isolated from the turmeric plant *Curcuma longa*. Curcumin has been reported in a plethora of studies to have anti-infectious, antioxidant, anti-inflammatory, hepatoprotective, cardioprotective, thrombo-suppressive, anti-arthritic, chemopreventive, and anticarcinogenic properties[10]. Studies have shown the therapeutic role of curcumin in various cancers, including oral cancer[11]. Curcumin acts on numerous molecular targets, including signal transducer and activator of transcription 3 (STAT3), activator protein 1 (AP-1), protein kinase B (PKB also known as Akt), Notch 1, nuclear factor κ-light chain enhancer of activated B cells (NF-κB), Wnt, mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR), and respective downstream signaling pathways, which are known to play key roles in oral cancer pathogenesis[10,12].

The hydrophobic nature of curcumin leads to poor bioavailability, and the sensitivity of soluble curcumin in physiological pH has limited its use in clinical practice[13]. However, nanotechnology-based techniques have made possible various novel formulations of curcumin such as liposomes, nanoparticles, micelles, phospholipid complexes, and analogues, to improve its tissue-level absorption and increase its pharmacological efficacy[14]. Studies have shown favorable results with the use of nano-formulated curcumin in the setting of epithelial cancers. Thus, it follows that curcumin may have a therapeutic role in oral cancer treatment as an adjuvant[15-17]. The present review aims to summarize the key properties of curcumin and its novel formulations, along with their role in oral cancer treatment.

**ORAL Cancer**

Oral cancer comprises neoplasms affecting any region of the oral cavity. The oral cavity is divided into distinct anatomic subsites, including lip, oral tongue, floor of the mouth, buccal mucosa, upper and lower gingiva, retromolar trigone, and hard palate[18]. However, 90% of oral cancers are histologically diagnosed as OSCCs[3]. OSCCs commonly present as nonhealing ulcers or growths. Early in the disease, lesions can appear as flat, discolored areas (*i.e.* erythroplakia or leukoplakia)[19]. Invasion of surrounding tissues can present with neck masses, trismus, referred ear pain, or specific sensory changes[20]. In cancer of the lip, there is often an exophytic, crusted lesion invading the underlying muscle with tissue damage in the adjacent lip[21]. Oral cancers are often diagnosed late due to an asymptomatic phase with fast progression and early metastasis[22]. Furthermore, the staging of oral cancer plays a significant role in survival rate, with early-stage (I and II) and advanced-stage (III and IV) lesions having a 5-year survival rate of 80% and 50% or less, respectively[22].

There are multiple pathways involved in oral carcinogenesis leading to genetic mutation (*e.g.,* H-ras, K-ras), gene deletions (*e.g.,* loss of chromosome 9p21 or 3p), promoter methylation (*e.g.,* p16, Ras association domain family member 1), amplification of oncogenes and oncoproteins (*e.g.,* EGFR, myc, bcl-2, ras, raf, stat-3, or cyclin D1) and inactivation of tumor suppressor genes (*e.g.,* p53)[23].

**PROPERTIES OF CURCUMIN**

Curcumin is a yellow spice derived from the roots (rhizomes) of *Curcuma longa*, commonly known as turmeric[24]. Turmeric contains curcuminoids, comprising curcumin, demethoxy curcumin (DMC), and bis-demethoxycurcumin (BDMC)[25]. In 1910, the principal ingredient of curcumin was identified by Gupta *et al*[26] as diferuloylmethane. Curcumin is known as 1, 7-bis (4-hydroxy-3-methoxy phenyl)-1, 6-heptadiene- 3, 5-dione (1E-6E) by International Union of Pure and Applied Chemistrynomenclature. It has a molecular weight of368.4 g/mol and a melting temperature of 183 °C[27].

Curcumin contains 2 aromatic ring systems with o-methoxy phenolic groups linked with α- and β-unsaturated β-diketone moiety (Figure 1)[28]. The absorption bands of curcumin exist in the visible spectrum (410 nm-430 nm) and the ultraviolet spectrum (250 nm–270 nm)[14]. At 488 nm, curcumin is excited by lower fluorescent yield emission in the 500 nm-530 nm range, which can be detected by flow cytometry and confocal microscopy[29]. Curcumin is insoluble in water and readily soluble in polar solvents with keto-enol tautomerism[30]. The keto-form predominates in acid or neutral solutions, with the enol-form being predominant in alkaline solutions[31].

 The bioavailability of curcumin is around 1% according to various animal studies, suggesting a requirement of high doses of curcumin (3600 mg to 12000 mg) to achieve beneficial effects[32]. It is known that curcumin’s solubility in water (0.0004 mg/mL at pH 7.3) is poor, giving rise to challenges with oral administration[33]. One study has shown that curcumin has no toxic effect in patients with colorectal cancer when its oral dose is at least 3600 mg[34]. Curcumin undergoes rapid metabolism in the liver and gets excreted in the feces[35]. Curcumin is transformed into dihydrocurcumin and tetrahydrocurcumin (THC) and consequently converted into glucuronide conjugates[36,37]. In intestinal mucosa, kidney, and liver, the conjugative enzyme activity for glucuronidation and sulfation of curcumin has been discovered[37,38]. Another study demonstrated that a considerable portion of orally administered curcumin was conjugated to glucuronide in the intestine; later, the conjugated compound entered the portal vein and underwent additional conjugation to form glucuronide/sulfate metabolites of curcumin in the liver[38].

Curcumin, having a vast range of effects on various human diseases, plays an anti-tumorigenic role in different cancers by affecting multiple pathways of cancer progression[10-12]. In addition, it has been shown to have different effects on normal cells *vs* cancer cells, including a higher uptake by cancer cells[39]. The anticancer effects of curcumin are predominantly mediated through its regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other oncogenic molecules, as summarized in Figure 2[10,11,33]. Curcumin metabolites (THC, hexahydrocurcumin, and octahydrocurcumin) also have anticancer properties[40,41]. However, the major factor restricting the use of curcumin as a novel chemotherapeutic agent is reduced bioavailability which is attributed to its poor absorption, rapid degradation, fast metabolism, and systemic elimination. Notably, as an anti-cancer drug, curcumin should be administered in a sufficiently high concentration; however, at these concentrations, patients have shown intolerance to bulk doses of the substance[33]. Using an advanced delivery system to increase the bioavailability of curcumin with satisfactory parenteral administration is the most promising solution to these challenges.

**EFFECTS OF CURCUMIN ON ORAL CANCER**

Curcumin is a potent agent that inhibits cell growth and deoxyribonucleic acid (DNA) synthesis in oral cancer cells[41]. Treatment with curcumin promotes the cell cycle’s G(2)/M phase arrest, accompanied by a decrease in cyclin B/cyclin-dependent kinase 1 and cell division cycle 25C protein levels. It induces apoptosis of oral cancer cells *via* reduction of Bcl-2 levels, reduction in mitochondrial membrane potential, promotion of the active forms of caspase-3, and the release of apoptosis-inducing factor (AIF) and endonuclease G from mitochondria[42]. Curcumin and curcuminoids like DMC and BDMC have shown autophagic and apoptotic activity[43,44].

Studies have shown that curcumin significantly inhibits the carcinogen-activating enzyme cytochrome P450 family 1 subfamily A member 1, which mediates benzo(a)pyrene diol bioactivation in both OSCC cells and oral mucosa[45]. Arecoline exposure is another significant risk factor for the development of oral cancer, and treatment with curcumin markedly inhibits arecoline-induced Snail expression[46]. One study showed that administration of curcumin at 100 mg/kg for 12 wk in a rat model with 4-nitroquinolone-1-oxide (4-NQO)-induced oral cancer markedly decreased the expression of proliferating cell nuclear antigen, anti-apoptosis markers (*e.g.,* Bcl-2), suppressors of cytokine signaling 3 and 1, and STAT3. It also minimized cellular atypia and reduced expression of vimentin, E-cadherin, N-cadherin, and TWIST1, which represent epithelial-mesenchymal transition (EMT) events[47]. Combining local and systemic C3 complex (a purified mixture of curcumin, BDMC, and DMC) effectively targets cancer cell proliferation. This combination inhibits 4NQO-induced tumorigenesis *via* modulation of fibroblast growth factor-2/fibroblast growth factor receptor-2[48]. Moreover, curcumin inhibits the activation and expression of host transcription factors AP-1 and NF-κB, which bind to a cis-regulatory region of the HPV genome. This effect is concentration- and time-dependent, leading to the suppression of HPV16/E6 transcription and the subsequent prevention of oral carcinogenesis[49]. Curcumin triggers the activation of p38, which then interacts with binding elements in insulin-like growth factor binding protein-5, leading to the activation of the transcription factor CCAAT/enhancer binding protein α (C/EBPα). This also results in the suppression of oral carcinogenesis[50].

Additionally, curcumin reduces oral cancer cell viability and invasion by downregulating Notch 1 and NF-κB[12]. It also induces G2/M phase cell cycle arrest in a dose-dependent fashion by inhibiting the phosphorylation of EGFR and its downstream signaling molecules Akt, extracellular signal-regulated kinase (ERK1/2), and STAT3[12]. Treatment of oral cancer cells with curcumin, BDMC, and DMC leads to the production of reactive oxygen species (ROS), activation of caspase-8, -9, and -3, a decrease in the levels of matrix metalloproteinases (MMP), the release of AIF, and an alteration in the expressions of EGFR, PI3K, p-AKT, NF-κB, AMP responsive protein kinase, and MAPK[44]. In an *in vivo* OSCC model, curcumin has also been observed to suppress the expression of cyclo-oxygenase-2[51].

The oncogenic microRNA miR-31 is upregulated in OSCC, and curcumin downregulates the expression of this molecule in OSCC, leading to an attenuation of AKT activation and downregulation of C/EBPβ[52]. Moreover, curcumin inhibits oral cancer cell proliferation by upregulating miR-9 expression in a dose-dependent manner and suppressing Wnt/β-catenin signaling[53]. Furthermore, curcumin can also enhance the antitumor immune response by inhibiting the expression of programmed cell death ligand 1 and pSTAT3 leading to an increase in CD8+ T-cells and a decrease in T regulatory cells and myeloid-derived suppressor cells[54]. Cancer-associated fibroblasts (CAFs) are activated fibroblasts in the tumor microenvironment that play a critical role in cancer development[55]. Curcumin can reverse the phenotype of CAFs to that of peri-tumor fibroblast-like cells by downregulating the expression of α-smooth muscle actin (a unique marker for CAFs) and inhibiting the secretion of pro-carcinogenic cytokines such as transforming growth factor-β1, MMP2, and stromal cell-derived factor-1[56]. This results in decreased cancer invasion, as evidenced by a reduced release of EMT mediators in treated CAFs and reversal of EMT in treated tumor cells[57].

Hepatocyte growth factor (HGF) signaling plays an important role in EMT induction and contributes to cancer cell invasion and metastasis[58]. Curcumin inhibits HGF-induced EMT and cell motility in oral cancer cells, acting on HGF receptor c-Met and blocking the downstream activation of the pro-survival ERK pathway[59]. It also decreases proliferation in cell lines with mesenchymal characteristics and causes cell death with a dose-dependent decrease in cell–cell adhesion[60]. Curcumin treatment has been found to suppress MMP-2, MMP-9, and MMP-10, which are linked to cancer cell migration and invasion in oral cancer[61,62].

Studies have shown that curcumin can enhance the efficacy of standard platinum-based chemotherapy for treating oral cancer, resulting in significant tumor growth suppression in cell lines and mouse xenografts[63,64]. These results highlight the potential of using subtherapeutic doses of cisplatin in combination with curcumin to effectively suppress tumor growth and minimize cisplatin’s toxic side effects.

Furthermore, curcumin has a radio-sensitizer effect in OSSC and exhibits synergistic antiproliferative activity when combined with cetuximab (an anti-EGFR monoclonal antibody) in cisplatin-resistant oral cancer cells[65,66]. A study of combinations of curcumin and metformin demonstrated a reduction in tumor volume and improvement of overall survival of experimental animals, as evidenced by downregulation of cancer stem cell markers CD44 and CD133[67]. Another study showed that olaparib (a poly-ADP ribose polymerase inhibitor), when combined with curcumin *in vitro* and *in vivo* (mouse model), causes DNA damage, inhibits cell proliferation and topoisomerase activity, reduces the expression of base excision repair components, induces apoptosis, and decreases tumor volume[68].

**CLINICAL TRIALS USING CURCUMIN FOR ORAL LESIONS**

Multiple clinical trials are ongoing or have been completed investigating the efficacy of curcumin against human diseases including oral pathologies. Kuriakose *et al*[69] conducted a study on oral leukoplakia, a potentially malignant oral cavity lesion with no effective treatment available. In this study, subjects with oral leukoplakia underwent a randomized, double-blinded, placebo-controlled phase IIB clinical trial with curcumin. Clinical and histological response assessments showed a significantly better outcome with curcumin treatment. Notably, the therapy was well-tolerated, and a significant and long-lasting clinical response was observed after treatment with curcumin at a dose of 3.6 g administered over 6 mo[69]. Furthermore, recent studies have shown that topical curcumin effectively treats oral mucositis[70]. Currently, a phase II randomized trial (double-blind, placebo-controlled) is ongoing to assess the therapeutic effects of curcumin in patients with stage III-IV head and neck cancer and cancer-associated anorexia-cachexia[71].

**NOVEL FORMULATIONS OF CURCUMIN IN ORAL CANCER TREATMENT**

***Curcumin analogues***

Several investigations have attempted to improve curcumin's therapeutic effectiveness and pharmacokinetic profile by developing new analogues[72,73]. The synthetic curcumin analogues that have been studied include the EF series (EF24, EF31, and UBS109), the FLLL series (FLLL11, FLLL12, FLLL31, FLLL32, and FLLL62), the GO-Y series, the 4-arylidene curcumin analogues AC17, B19 [(1E,4E)-1,5-bis(2,3-dimethoxy phenyl) penta-1,4-dien-3-one], CDF (difluorinated curcumin), and 4-[3,5-bis(2-chlorobenzylidene-4-oxo-piperidine-1-yl)-4-oxo-2-butenoic acid] CLEFMA, the diarylidenylpiperidones series, DM-1 (sodium 4-[5-(4-hydroxy-3-methoxyphenyl)-3-oxo-penta-1,4-dienyl]-2- methoxy phenolate), and dimethoxycurcumin[74]. In addition, some of these new analogues have been reported to have more potent anticancer properties than curcumin, and may have more beneficial antioxidant, antimalarial, and anti-inflammatory properties than the parent compound[75-79].

A few analogues including EF24, CDF, and FLLL12, exhibit enhanced physicochemical properties such as improved solubility and bioavailability, allowing them to overcome the limitations of curcumin[80,81]. In addition, some analogues have shown to increase the efficacy of chemotherapeutic agents and to overcome issues of resistance when combined therapy is used[82,83]. These analogues have shown promising results in breast, prostate, colon, and head-neck squamous cell cancers[77,84-87]. In a study of oral cancer cells, Chuprajob *et al*[88] found that curcumin analogues with the 1,4,6-trien-3-one function are more potent than the curcuminoid types. Also, structural variations in the analogues enhanced their potency; for example, the meta-oxygen function of the aromatic ring is more potent than those in the ortho and para positions, and the free phenolic hydroxy group is more potent than in the corresponding methyl analogues[88]. Furthermore, some analogues showed fewer toxic effects than curcumin when applied to normal cells[88]. In 2017, Lin *et al*[89] found that EF24 exhibited antitumor activity on CAL-27 oral cancer cells by deactivating the MAPK/ERK signaling pathway.

Several curcumin analogues have been developed in recent years, and most of the analogues have shown mechanisms of action similar to that of curcumin. However, some have unique mechanisms that are not associated with curcumin. For instance, the B19 analogue inhibits thioredoxin reductase 1, leading to ROS-mediated endoplasmic reticulum stress, whereas the AC17 analogue blocks proteasome function by inhibiting the deubiquitinase activity of 19S regulatory particles; neither of these mechanisms are seen with curcumin[90,91]. Further studies are required to evaluate the specific benefits of these inhibition pathways in cancer treatment.

Despite their promising potential, key parameters for the clinical development of many promising analogues remain unknown, and further attention should be given to the study of their pharmacokinetics. To reduce drug-associated toxicities and improve bioavailability, targeted drug delivery through alternative formulation has been gaining attention. Some studies have shown that curcumin analogues can be conjugated to homing moieties to direct their delivery and accumulation at specific sites. Certain homing moieties have been tested, including hyaluronic acid (HA)-targeted nanomicelles, HA dendrimers, folic acid-conjugated CDF, and EF24 conjugated to coagulation factor VIIa to target tissue factor[92-95]. These potential agents have yet to undergo clinical trials and cost-effective production strategies. Further *in vivo* studies can pave the way for clinical trials and future applications.

***Nanoformulations of curcumin***

Nanotechnology has led the way in developing nanoscale drug delivery systems. Hydrophobic molecules such as curcumin can benefit from improved bioavailability as a result of the surface, small size, quantum size, and quantum tunnel effects of nanoparticles[96,97]. Several novel strategies have been developed to design curcumin nanoparticles as targeted drug-delivery systems, and these have been studied in various disease states, including cancer[33] (Figure 3).

The following is a summary of the different nanotechnology-based drug delivery modalities for potential use with curcumin.

**Liposomes:** These are spherical, closed phospholipid vesicles that incorporate drugs in the inner aqueous layer and have been widely used to enhance the bioavailability and efficacy of curcumin. In recent years, several liposomal curcumins with polymeric conjugates have been modified to achieve better clinical outcomes[98].Nanoliposomes have shown properties such as sustained drug release, enhanced tumor targeting, minimized toxicity to healthy cells, and a lower dose[99].

**Polymer micelles:** These represent an excellent drug delivery system for curcumin, as they can overcome issues with poor solubility, low stability, and poor bioavailability. Encapsulating curcumin within cationic micelles like cetyltrimethylammonium bromide or dodecyl trimethyl ammonium bromide can enhance drug loading capacity, increase water solubility, reduce toxicity, and limit degradation[100]. Nanomicelle curcumin has been shown to prevent and treat oral mucositis caused by head and neck radiotherapy and chemotherapy[101,102].

**Polymer nanoparticles:** Polymer nanoparticles are another effective drug delivery system, owing to their high biocompatibility and ease of circulation in the bloodstream for longer periods. Synthetic polymer conjugates such as chitosan, d,l-lactide-co-glycolide (PLGA), polyethylene glycol (PEG), poly (n-butyl) cyanoacrylate, silk fibroin, N-isopropyl acrylamide, and hydrophobically modified starch are commonly used. Curcumin-loaded nanoparticles using PEG-5000 as a carrier stabilizer for PLGAs have shown results in mouse models of cancer, with higher cellular uptake and induction of apoptosis both *in vitro* and *in vivo*[103].

**Solid lipid nanoparticles:** Solid lipid nanoparticles consist of natural lipids (*e.g.,* lecithins or triglycerides) that remain solid at 37 °C. These molecules protect labile compounds from chemical degradation and improve bioavailability. Curcumin-loaded solid lipid nanoparticles have shown enhanced cellular uptake and are promising anticancer agents against breast cancer cells *in vitro*[104].

**Inclusion complexes:** Inclusion complexes are formed of cyclodextrins and cyclic oligosaccharides composed of 6 to 8 glycosyl monomeric units (α-1,4 linked). They are widely used to improve stability, enhance water solubility, increase bioavailability, and reduce bitterness. β-Cyclodextrin is commonly used to form an inclusion complex with curcumin by solvent evaporation or pH shift techniques[105].

**Solid dispersions:** Solid dispersions have improved curcumin's physicochemical and pharmacokinetic activities. Wet-melting and subsequent freeze-drying are common strategies for preparing crystal and amorphous forms in which curcumin is dispersed in an inert carrier at a solid-state[106].

**Magnetic nanoparticles:** Drug-loaded magnetic nanoparticles can be directed to cancer-affected tissues under external magnetic fields to offer a targeted drug delivery option. Entrapping curcumin in an Fe3O4-curcumin conjugate with oleic acid or chitosan in the outer shell results in the formation of nano-sized, fluorescent-magnetic, water-dispersible nanoparticles with increased cellular uptake and enhanced bioavailability[107].

**Microspheres and microcapsules:** This approach encapsulates drugs or molecules like curcumin within polymeric particles to improve efficacy and organ-targeted bioavailability. Particles that have been used include camptothecin, rutin, zedoary oil, andrographolide, and eudragit S-100[108].

**Emulsions:** Emulsions refer to small-droplet dispersions comprising of oil and water mixtures that are stabilized by surfactant molecules to form interfacial films. These represent a lipid-based drug delivery system possessing numerous advantages, including thermodynamic stability, improved drug dissolution, and increased solubility[109]. High-speed and high-pressure homogenization procedures using triacylglycerol and Tween-20 as emulsifiers produce tiny microemulsion droplets. Incorporating curcuminoids into nanoemulsions has been shown to increase oral bioavailability[110].

**Nanogels:** Nanogels are 3-dimensional polymer networks with high drug loading capacity, high dispersion stability, targeted drug delivery efficiency, fast drug releasing properties, and increased drug delivery across cellular barriers. Moreover, they are easy to modify chemically. Curcumin has been used as a nanogel for targeted therapy[111].

**Nanoparticle curcumin:** Nanoparticle curcumin is a pure form of curcumin that is processed into nanoparticles of approximately 200 nm in size without carrier conjugates. *In vitro* and *in vivo* studies have shown that these nanoparticles of curcumin exhibit increased cellular uptake and enhanced anticancer effects due to their size, surface charge, and surface area[112-114].

**Niosomes:** Niosome nanocapsules are drug carriers composed of non-ionic surfactants that form a bilayered structure with hydrophobic and hydrophilic parts in an aqueous medium. Niosomes offer numerous advantages, including improved pharmacokinetics, drug stability, therapeutic effects, and reduced side effects of the administered drug[115].

Using nanoformulation-based combination therapy has gained popularity as a potent drug delivery system, often overcoming the limitations of conventional therapeutic agents. This delivery system has shown to improve intracellular drug concentrations and enhance the synergistic activity for cancer therapy[116-118]. Specific curcumin novel formulations have been studied for their efficacy in treating oral cancer, with encouraging findings (Table 1)[119,120].

In 2012, Lin *et al*[121] conducted a study to assess the effects of curcumin microemulsion on oral cancer cell lines. They found that exposure to curcumin-containing microemulsions for a brief period produced cytotoxic effects in the cancer cells. However, adding ultrasound enhanced these effects in OSCC-25 cells[121]. This observation is likely attributable to enhanced curcumin delivery to the cell by the fusion of microemulsion droplets with cell membranes or by overcoming transport limitations *via* ultrasound-induced mixing and/or heating. These ingestible microemulsions can be therapeutic in concentration-adjusted doses and have tissue-targeting properties when combined with ultrasound. Studies have shown that curcumin nanoparticles (Cur-NPs) possess significantly greater bioavailability and water solubility than free curcumin[122,123]. In a 2013 study by Chang *et al*[103] investigating CAL27-cisplatin-resistant human oral cancer cells (CAR cells), water-soluble PLGA Cur-NPs enhanced the drug effect. Cur-NPs increased ROS production, upregulated the expression levels of cleaved caspase-3/caspase-9, cytochrome c, apoptotic protease activating factor-1, AIF, and Bax, and downregulated the expression of Bcl-2. Cur-NPs also triggered the intrinsic apoptotic pathway by regulating the function of multiple drug resistance proteins 1 (MDR1) and the production of ROS in CAR cells[103]. Previous studies have also reported that MDR1 (a cell surface permeability glycoprotein) is a significant target of Cur-NPs[124,125]. In this study, treatment with Cur-NPs decreased MDR1 mRNA and protein levels in CAR cells, indicating the induction of CAR cell apoptosis, representing a potential treatment for cisplatin-resistant oral cancer.

Curcumin is phototoxic in the presence of oxygen[126,127]. Singh *et al*[128] demonstrated the use of organically-modified silica nanoparticles (SiNps) as a vehicle for the delivery of curcumin in human oral cancer cells. The results showed improved uptake of curcumin and phototoxicity in cancer cells. Incubation time-dependent cytotoxicity, inhibition of NF-κB activity, suppression of NF-κB-regulated proteins involved in invasion (MMP-9), angiogenesis (*via* vascular endothelial growth factor), and inflammation (tumor necrosis factor α) were observed with curcumin-SiNp. These results suggest that the curcumin–SiNp formulation has significantly improved anti-cancer effects over free curcumin in the dark and upon exposure to light[128]. These findings are likely the result of increased oxidative stress induced in the cancer cells upon visible light exposure in the presence of oxygen. The curcumin–SiNp formulation also enhances the stability of curcumin at physiological pH and increases its aqueous solubility.

In 2015, Mazzarino *et al*[129] conducted a study on the effect of mucoadhesive polycaprolactone (PCL) nanoparticles coated with chitosan and loaded with curcumin as a treatment for oral cancer. This study used the nanoprecipitation method to prepare the chitosan-coated PCL nanoparticles with curcumin loading[130]. The nanoparticles showed mucoadhesive properties, as evidenced by interaction with the glycoprotein mucin through electrostatic forces. *In vitro* studies showed that these novel curcumin nanoparticles significantly decreased the viability of SCC-9 human oral cancer cells by inducing apoptosis[129]. The study also suggested that drug retention in the mucosa after treatment with chitosan-coated curcumin-loaded nanoparticles could be helpful for local therapy in numerous diseases.

Gold nanorods (GNRs) are known for their photothermal activity and inherent tumor-targeting properties[131]. In 2018, Zhu *et al*[132] developed a novel system for combined plasmonic photothermal therapy and chemotherapy using the tumor microenvironment and near-infrared responsive gold nanorod-drug conjugates (Au NR@Curcumin). This study tested the antitumor effects of Au NR@Curcumin on human lung, liver, and oral carcinoma cells and found that it showed more potent cytotoxicity than the free drug. Additionally, oral cancer cells demonstrated cell cycle S phase arrest. The study suggested that Au NR@Curcumin could be effective at inducing instant photothermal killing of the cancer cells, even at a low irradiation power density[132]. In 2020, Ghosh *et al*[133] developed a multimodal nanoconjugate by functionalizing the GNR surface with a cytotoxic nucleoside [5-fluoro-2′-deoxyuridine (FdU)]-containing DNA hairpin followed by hydrophobic complexation of curcumin. This study showed that curcumin could be noncovalently complexed into small DNA hairpins for enhanced cellular delivery. This system caused increased cytotoxicity in SCC 131 oral cancer cells when administered in combination with FdU nucleotides, demonstrating its potential for advanced cancer therapy[133].

Several studies have investigated the potential of curcumin nanoparticles in combating oral cancer. Srivastava *et al*[112] found that Nano-CU, a curcumin nanoparticle, exhibited chemoprotective properties against 5-fluorouracil-induced toxicity in oral cancer cells. Nano-CU was found to have an antioxidant effect, and altered the expression of apoptotic proteins Bcl-2 and Bax in treated cells[112]. Another study by Lai *et al*[134] explained the anticancer properties of gefitinib (Gef) and curcumin-loaded NPs in human oral cancer SAS cells *in vitro* and SAS cell xenografted tumors *in vivo*. The results indicated that γ-polyglutamic acid-coated (PGA)-Gef/Cur NPs could be internalized into SAS cells and significantly decrease the total cell viability. Both free Gef/Cur and γ-PGA-Gef/Cur NPs induced apoptotic cell death *via* caspase-3, caspase-9, and mitochondria-dependent pathways. *In vivo* studies showed that γ-PGA-Gef/Cur NPs significantly suppressed tumor size compared to the free Gef/Cur-treated group[134]. In 2022, Essawy *et al*[135] developed nanoparticle curcumin using a more straightforward and cost-effective solvent-antisolvent precipitation technique and studied its effect on oral cancer cells. This study found promising cytotoxic results *via* apoptosis in contrast to the necrotic effect observed using doxorubicin in the cell lines. The authors also reported the observed luminescence of the nanoparticle curcumin, qualifying it as a double theranostic agent[135]. In another study, co-treating oral cancer cells with nanoparticle curcumin (approximately 200 nm size) and cetuximab showed higher cytotoxicity than cetuximab alone[136]. The above mentioned studies highlight the potential chemo-adjuvant role of curcumin nanoparticles in combating oral cancer.

In 2019, Ferreira *et al*[137] aimed to develop nanostructured gel formulations containing curcumin for oral cancer therapy. The authors showed that the use of this novel curcumin led to rapid incorporation and localization in the hydrophobic portion of nanometer-sized polymeric micelles, resulting in increased retention after application in the oral cavity. Cytotoxicity testing showed that the formulation selectively targeted cancer cells moreso than healthy cells. Therefore, these systems may improve the physicochemical characteristics of curcumin by increasing its release and permeation and enhancing its cancer cell-targeting properties[137]. Recently in 2022, Fazli *et al*[138] found that curcumin-loaded niosomes significantly inhibited the growth and necrosis of oral cancer cells compared to free curcumin. Histopathological specimens from rats with induced oral cancer showed that niosome curcumin treatment effectively inhibited cancer growth. The authors also highlighted that the injectable curcumin-loaded niosome (*i.e.* for systemic use) was more effective than the mouthwash form of application (*i.e.* for topical use)[138]. In light of these promising findings, future studies should be designed to explore the outcomes of novel curcumin formulations in preclinical and clinical trials.

**CHALLENGES AND FUTURE DIRECTIONS**

Oral cancer is a highly malignant disease with a poor 5-year survival rate and limited treatment options, underscoring the importance of adjuvant therapy. Curcumin, known for its pleiotropic effects and potential therapeutic benefits, has shown promise as a treatment choice for patients with cancer. This molecule has shown improvement in the efficacy of current cancer therapeutics, including overcoming the resistance of cancer cells to chemo-radio therapy. However, several clinical and practical challenges need to be addressed before curcumin can be incorporated into regular clinical practice. The purity of the curcumin compound significantly affects its activity, and is of primary importance when used in studies or trials[139]. In addition, body tissue distribution and uptake of curcumin, which account for its biological activity, need better understanding[31]. Clinical trials with curcumin have faced various challenges, such as high metabolic instability, poor aqueous solubility, inadequate focalization, complex pharmacokinetic profile, and poor patient adherence[140].

Nanotechnology-based formulations and analogues have shown potential in overcoming the poor bioavailability issue of curcumin by improving its stability, increasing its cellular uptake, and offering controlled release. However, these formulations often lack tissue specificity. Although the various novel nano-formulations of curcumin show remarkable anti-neoplastic, theranostic, and chemo-adjuvant properties, there are technical challenges in drug development, particularly the need to regulate the size of curcumin nanoparticles for drug delivery applications. In addition, these processes are expensive and have yet to be commercialized. The effects of newer delivery systems, such as polymer nanoparticles and liposomes, on the therapeutic efficacy of curcumin need to be further investigated; while these have been shown to enhance curcumin bioavailability, the possibility of off-target toxicity has not been thoroughly studied[141]. Curcumin has shown cytotoxic and cytoprotective effects at different doses and concentrations in various cancer studies[112,135,142,143]. These findings need consideration in preclinical and clinical trials investigating newer curcumin formulations. Furthermore, the wide range of research variability in human cancer studies using these novel curcumin formulations, such as differences in study design, drug design, sample size, and route of administration, also make it difficult to conclude which formulation has the best overall pharmacokinetic properties[140].

**CONCLUSION**

In conclusion, encouraging findings from various studies using novel curcumin formulations indicate the need for extensive preclinical and clinical research to shed light on their pharmacokinetics, biocompatibility, toxicity, and dose regimens in normal and disease conditions in order to incorporate these agents in cancer treatment strategies. Systematic efforts must focus on identifying a potential curcumin formulation suitable for use in clinical trials. Collaboration between clinicians, translational scientists, medicinal chemists, and pharmacologists is necessary to advance these agents toward clinical use as oral cancer therapeutics.

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**Footnotes**

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**Figure Legends**



**Figure 1 Chemical structure of curcumin.**



**Figure 2 Effects of curcumin on multiple molecular targets involved in carcinogenesis.** ↑: Upregulated; ↓: Down regulated. AP-1: Activator protein 1; AR: Androgen receptor; CREB BP: CREB Binding protein; CXCR: Chemokine receptor; DR4, DR5: Death receptor 4, 5; EGF: Epithelial growth factor; EGFR: Epithelial growth factor; EPCR: Endothelial cell protein C receptor; ERE: Estrogen response element; FADD: FAS-associated death domain; Fas R: Fas receptor; FGF: Fibroblast growth factor; FPT: Farnesyl protein transferase; GST: Glutathione S transferase; HGF: Hepatocyte growth factor; HIF 1: Hypoxia inducible factor 1; iNOS: Inducible Nitric oxide synthase; IR: Insulin receptor; JNK: Jun N-terminal kinase; LDLR: Low density lipoprotein receptor; MAPK: Mitogen activated protein kinase; MCP: Monocyte chemo-attractant protein; MIP: Macrophage inflammatory protein; MMP: Matrix metalloproteinase; NQO-1: NAD(P)H dehydrogenase (quinone) 1; NRF 2: Nuclear factor erythroid 2-related factor 2; PARP: Poly ADP- Ribose polymerase; PCNA: Proliferating cell nuclear antigen; PDGF: Platelet derived growth factor; PK: Protein kinase; PPAR γ: Peroxisome proliferator-associated receptor γ; STAT: Signal transducer and activator of transcription; TGF β 1: Transforming growth factor β 1; TNF-α: Tumor necrosis factor α; VEGF: Vascular endothelial growth factor.



**Figure 3 Nanoformulations of curcumin used in various studies.**

**Table 1 Oral cancer studies with novel curcumin formulations**

|  |  |  |  |
| --- | --- | --- | --- |
| Curcumin formulations | Study type | Results | Ref. |
| Liposomes | In vitro | Size of vesicle attributed to enhanced release of curcumin and cytotoxicity in the SCC9 cells | Gosangari et al[119], 2012 |
| Cur microemulsion | In vitro | Damaged and ruptured OSCC 25 cells, cell death enhanced by ultrasound | Lin et al[121], 2012 |
| PLGA Cur- NP | In vitro | Increased ROS production, upregulated caspase-3/caspase-9, cytochrome c, Apaf- 1, AIF, Bax, downregulated Bcl-2 | Chang et al[103], 2013 |
| Cur-SiNP | In vitro | Cytotoxicity by inhibition of NF-κB activity, suppression of MMP-9, angiogenesis (VEGF), and inflammation (TNF-α) in the dark as well as on exposure to light | Singh et al[128], 2014 |
| Trienone analogues of curcuminoids | In vitro | 1,4,6-trien-3-one analogue has more potent cytotoxicity than the curcuminoid type function in oral cancer cells | Chuprajob et al[88], 2014 |
| Cur-loaded chitosan-coated PCL nanoparticle | In vitro | Mucoadhesive properties decreased SCC9 cell viability by inducing apoptosis | Mazzarino et al[129], 2015 |
| Cur analogue EF24 | In vitro | Anticancer activity on CAL-27 cancer cells via deactivation of the MAPK/ERK signaling pathway | Lin et al[89], 2017 |
| Gold nanorod-drug conjugates (Au NR@Curcumin) | In vitro | Cancer cell cycle S phase arrest, the photothermal killing of the cancer cells | Zhu et al[132], 2018 |
| NP Cur | In vitro | Chemoprotective nature of Cur towards 5-FU induced cell toxicity, antioxidant effect, altered expression of apoptotic proteins Bcl2 and Bax | Srivastava et al[112], 2018 |
| In vitro | Chemo-adjuvant property of NP Cur with Cetuximab | Mukherjee et al[136], 2022 |
| In vitro | Cytotoxicity via apoptosis, luminescence property of NP Cur acting as a theranostic agent | Essawy et al[135], 2022 |
| PGA- Gef/Cur NP | In vitro | NPs internalized into SAS cells, decreased cell viability, and induced apoptotic cell death via | Lai et al[134], 2019 |
| caspase-3,9 and mitochondria-dependent pathway |
| In vivo | Suppressed tumor size compared to the free Gef/Cur-treated group |
| Mucoadhesive nanostructured Cur | In vitro, Ex vivo | Improved cytotoxicity, enhanced Cur release, and permeation while selectively targeting cancer cells | Ferreira et al[137], 2019 |
| DNA Cur complex | In vitro | Enhanced cellular delivery of Cur increased cancer cell cytotoxicity in combination with FdU nucleotides | Ghosh et al[133], 2020 |
| Nano micelle | In vitro | Improved controlled-release of Cur, enhanced cellular uptake, apoptotic cell death by changing the mitochondrial membrane potential | Kumbar et al[120], 2022 |
| Cur |
| Cur-loaded noisome | In vitro | Significant cytotoxicity compared to free curcumin after 24 h | Fazli et al[138], 2022 |
| In vivo | Injection use (systemic) was shown to be more effective than the use of mouthwash (topical) |

AIF: Apoptosis-inducing factor; Apaf-1: Programmed cell death ligand 1; CAR cells: Cisplatin-resistant human oral cancer cells; Cur: Curcumin; FdU: 5-fluoro-2′-deoxyuridine; 5-FU: 5-fluorouracil; MAPK: Mitogen-activated protein kinase; MDR 1: Multiple drug resistance proteins 1; MMP-9: Matrix metalloproteinase 9; Nano-CU: Nanoparticle of curcumin; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; NP: Nanoparticle; OSCC: Oral squamous cell carcinoma; PCL: Polycaprolactone; PGA- Gef/Cur NP: γ-polyglutamic acid-coated Gefitinib and curcumin-loaded nanoparticles; PLGA: D,l-lactide-co-glycolide; ROS: Reactive oxygen species; SCC: Squamous cell carcinoma; SiNp: Silica nanoparticle; TNF-α: Tumor necrosis factor α; VEGF: Vascular endothelial growth factor.



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