

Overcoming the "Bioavailability" Barrier: Novel Delivery Systems for Oral Cancer

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies, with a five-year survival rate persistently below 50% despite surgical, chemo-, and radiotherapeutic advances. Curcumin, the principal curcuminoid (~77%) of turmeric (*Curcuma longa* L.), has demonstrated preclinical activity against OSCC through inhibition of NF- κ B, STAT3, VEGF, and apoptotic pathways. However, its clinical translation is severely restricted by less than 1% oral bioavailability, rapid metabolic degradation, and instability at neutral and alkaline pH. Turmeric contains two additional pharmacologically active curcuminoids — demethoxycurcumin (DMC, ~18%) and bisdemethoxycurcumin (BDMC, ~5%) — both of which possess demonstrably greater chemical stability and superior pharmacokinetic profiles compared to curcumin, owing to the absence of one or both methoxy groups. Despite established mechanistic evidence of their activity in OSCC-relevant protein targets, DMC and BDMC remain systematically absent from OSCC-targeted drug delivery research.

Objective: This review presents, for the first time, a structured evidence synthesis mapping the mechanistic activity of DMC and BDMC against specific OSCC protein targets across ten established drug delivery platforms, and explicitly identifies the translational gaps created by their systematic exclusion from OSCC delivery research.

Methods: A comprehensive, PubMed-indexed literature review was conducted across ten delivery subtopics — mucoadhesive buccal patches, nano-liposomal encapsulation, pH-responsive nanoparticles, photodynamic therapy (PDT), niosomes, exosome-based carriers, in situ gelling systems, piperine-curcumin synergistic complexes, and clinical translation pathways — evaluating available mechanistic, pharmacokinetic, in vitro, and in vivo evidence for

DMC and BDMC specifically in oral cancer contexts. All included references are peer-reviewed and directly traceable to cited sources.

Key Findings: DMC was identified as the single most effective anti-tumour compound among 639 natural products screened against OSCC cells, operating via USP13-mediated stabilisation of PTEN and consequent suppression of the PTEN/Akt/HK2 glycolytic axis — a mechanism not reported for curcumin in OSCC. DMC additionally induces G2/M arrest and caspase-mediated apoptosis via the p38 MAPK–HO-1 axis in HSC-3 and SCC-9 tongue carcinoma cell lines, suppressing cIAP1 and XIAP — key mediators of cisplatin resistance — and demonstrating synergy with gefitinib in OSCC. DMC further inhibits NF- κ B-driven apoptotic signalling in FaDu pharyngeal squamous carcinoma cells and overcomes cisplatin resistance via ERCC1 suppression through the PI3K-Akt-Snail pathway when delivered in chitosan nanoparticles. BDMC demonstrated superior anti-invasion and anti-angiogenic activity compared to curcumin in head and neck squamous carcinoma models through simultaneous suppression of NF- κ B, STAT3, VEGF, MMP-9, TGF- β , and multiple EMT regulators. BDMC also suppressed Bcl-2 and XIAP while upregulating BAX and caspase-3 in glioblastoma xenograft models, inhibited NF- κ B-mediated invasion via GRB2/RhoA/uPA in cervical carcinoma, and suppressed GPR161/mTOR-driven EMT in triple-negative breast cancer. Critically, BDMC has been confirmed to generate reactive oxygen species — hydroxyl radicals and singlet oxygen — under blue light irradiation, establishing proof-of-concept for its application as a photosensitiser in OSCC-directed PDT.

Gaps Identified: Across all ten delivery subtopics reviewed, neither DMC nor BDMC has been incorporated into a delivery system specifically designed for OSCC. No mucoadhesive buccal film or patch, pH-responsive nanoparticle, liposome, exosomal carrier, or in situ gel has been formulated with either molecule as the active payload for oral cancer. No BDMC-PDT study exists in any human cancer cell line,¹ and no DMC-PDT study exists in any model. The piperine–DMC/BDMC pharmacokinetic interaction is entirely unstudied. No comparative pharmacokinetic study of all three curcuminoids exists in an OSCC-relevant oral delivery model. The complete clinical translation pathway — from OSCC-specific in vitro validation through Phase I trials — is absent for both molecules. Exosomal delivery, pH-responsive nanoparticles, and PDT applications represent the three highest-priority unstudied combinations based on mechanistic rationale and platform suitability.

DMC and BDMC represent a neglected pharmacological resource in OSCC therapy development. This review establishes the evidence-based framework for redirecting OSCC curcuminoid delivery research from its current curcumin-centric focus toward the more potent, more stable, and mechanistically distinctive minor curcuminoids. Immediate research priorities include OSCC-specific in vitro validation of BDMC in HSC-3, SCC-9, and CAL-27 cell lines, DMC/BDMC formulation into established OSCC delivery platforms, and initiation of BDMC-PDT studies — steps with direct implications for the field's ability to translate preclinical curcuminoid activity into effective oral cancer therapeutics.

Keywords: *demethoxycurcumin; bisdemethoxycurcumin; oral squamous cell carcinoma; drug delivery; nanoparticles; photodynamic therapy; PTEN; NF- κ B; gap analysis; curcuminoids*

1. Introduction: The Curcuminoid Selectivity Problem in OSCC

Oral squamous cell carcinoma (OSCC) accounts for over 90% of all oral malignancies, with a 5-year survival rate persistently below 50% despite surgical, chemo- and radiotherapeutic advances. [1] The therapeutic landscape for OSCC continues to be defined by resistance to cisplatin, toxicity from radiotherapy, and lack of molecularly targeted options beyond cetuximab. [2]

Turmeric (*Curcuma longa* L.) has been the subject of extensive preclinical investigation for oral cancer. Curcumin, the principal curcuminoid (~77% of commercial turmeric extract), has been shown to inhibit NF- κ B, STAT3, VEGF, and numerous apoptotic pathways in OSCC cell lines. [3] However, curcumin's clinical translation is hampered by its extreme metabolic instability — with <1% oral bioavailability — and its known instability at neutral and alkaline pH. [4]

Turmeric contains not one but three pharmacologically active curcuminoids: curcumin (~77%), demethoxycurcumin (DMC, ~18%), and bisdemethoxycurcumin (BDMC, ~5%). [5] Critically, DMC and BDMC possess demonstrably greater chemical stability than curcumin owing to the absence of one or both methoxy groups — a structural difference that profoundly affects metabolic susceptibility, aqueous solubility, and protein-binding affinity. [6]

Despite this established pharmacological rationale, the overwhelming majority of delivery systems developed for OSCC — including mucoadhesive patches, nanoliposomes, pH-responsive nanoparticles, niosomes, and photosensitizer platforms — have been formulated exclusively with curcumin as the active payload. DMC and BDMC remain systematically absent from OSCC-targeted delivery research. This review presents, for the first time, a structured evidence synthesis mapping the mechanistic activity of DMC and BDMC against specific OSCC proteins across ten delivery modalities, and explicitly identifies the translational gaps this absence creates.

2. Molecular Properties of DMC and BDMC vs Curcumin: Why the Difference Matters

2.1 Structural Pharmacology

Curcumin (diferuloylmethane) bears two methoxy groups on its phenyl rings. In DMC, one methoxy group is replaced by a hydrogen atom, while in BDMC, both methoxy groups are absent. [6] This structural simplification confers three key pharmacological advantages.

First, DMC demonstrates better stability than curcumin after oral ingestion and significantly higher aqueous solubility, making it a more pharmacokinetically viable compound. [7] Second, BDMC has been identified as the most chemically stable of the three curcuminoids, with lower leakage rates in niosomal formulations (below 2% in 45 days under optimized conditions versus curcumin's rapid degradation). [8] Third, the removal of methoxy groups alters the electronic character of the β -diketone moiety, modifying hydrogen-bond donor-acceptor interactions with target proteins — a difference with direct implications for binding affinity to NF- κ B, cIAP1/XIAP, and PTEN.

2.2 Comparative Potency Ranking

A 2009 study by Limtrakul et al. established through differential invasion assays that the anti-metastatic ranking of the three curcuminoids follows: BDMC \geq DMC > Curcumin. [9] This ranking has been subsequently supported by independent investigations in non-oral cancer models. [10]

In a landmark natural product screen of 639 compounds conducted specifically against OSCC cells, Liao et al. (2025) identified DMC — not curcumin — as the single most effective anti-tumor compound, operating via inhibition of Hexokinase 2 (HK2)-mediated glycolysis through stabilization of PTEN and suppression of the PTEN/Akt/HK2 pathway. [11] This finding positions DMC as potentially superior to curcumin for OSCC, yet no delivery system has been designed to exploit this selectivity.

Table 1: Comparative ADMET and pharmacological profile of curcumin, DMC, and BDMC

Property	Curcumin	DMC	BDMC
MW (g/mol)	368.38	338.35	308.33
LogP	3.29	3.10	2.86
Aqueous solubility	Very poor (logS -4.2)	Poor but better than curcumin	Most stable in curcuminoid mixtures
Lipinski compliance	Violates (>10 rotatable bonds)	Passes all rules	Passes all rules
Metabolic stability	Rapid glucuronidation/sulfation	Greater stability than curcumin	Most chemically stable
Oral bioavailability	<1%	Higher than curcumin (inferred)	Stable in formulations
OSCC-specific protein screen	Multiple studies	Most effective of 639 compounds (PTEN/Akt/HK2)	Superior anti-invasion (BDMC \geq DMC > Cur)
Key references	[4,5,6]	[6,7,11]	[5,8,9,10]

Sources: [4] Anand et al., 2007; [5] Hewlings & Kalman, 2017; [6] Hatamipour et al., 2021; [7] Wang et al. (Frontiers Pharmacol); [8] Li et al., 2017; [9] Limtrakul et al., 2009; [11] Liao et al., Cancer Gene Ther, 2025.

3. Demethoxycurcumin (DMC) in OSCC: Established Mechanistic Evidence

3.1 G2/M Arrest and Caspase Cascade via p38 MAPK–HO-1 Axis

The most direct mechanistic characterization of DMC in OSCC was provided by Tseng et al. (2020) in a study using HSC-3 and SCC-9 tongue squamous carcinoma cell lines. [7] DMC induced G2/M phase cell cycle arrest in a concentration-dependent manner at 12.5–50 μ M, reducing G0/G1 cell fractions while significantly expanding the G2/M compartment. Total apoptotic rates in DMC-treated HSC-3 cells ranged from 8.9–52.2%, compared with 5.1–46% in SCC-9 cells.

Mechanistically, DMC downregulated cellular inhibitor of apoptosis 1 (cIAP1) and X-linked inhibitor of apoptosis protein (XIAP) — both survival proteins frequently overexpressed in cisplatin-resistant OSCC — while upregulating heme oxygenase-1 (HO-1). The p38 MAPK pathway was identified as the upstream regulator: p38 inhibition abolished DMC-induced HO-1 expression and blocked caspase-8, -9, and -3 activation. [7]

Critically, a combinatorial treatment of DMC with gefitinib (EGFR tyrosine kinase inhibitor) significantly enhanced the antiproliferative effect in OSCC cells, suggesting that DMC-mediated cIAP1/XIAP suppression sensitizes cells to EGFR-targeted therapy — a synergy currently unexploited in any delivery platform. [7]

3.2 NF- κ B Inhibition in Head and Neck Squamous Carcinoma

Lee et al. (2022) demonstrated that DMC induces apoptosis in FaDu human pharyngeal squamous cell carcinoma cells through NF- κ B pathway inhibition. [12] NF- κ B p65 is constitutively active in 70% of OSCC cases and drives resistance to chemotherapy and radiotherapy. DMC's inhibition of this pathway in HNSCC models directly addresses one of the most clinically significant resistance mechanisms in OSCC therapy.

The same study confirmed caspase-dependent apoptotic cell death, corroborating the HSC-3/SCC-9 findings. Together these data establish NF- κ B and the caspase cascade as the primary protein-level effectors of DMC action in squamous carcinoma of the oral and pharyngeal region.

3.3 PTEN/Akt/HK2: A Novel DMC-Specific Pathway in OSCC

The most recent and arguably most significant OSCC-specific mechanistic study on DMC was published by Liao et al. in *Cancer Gene Therapy* (2025). [11] From a library of 639 natural products screened against OSCC cells, DMC emerged as the single most effective anti-tumor agent. The mechanism involved DMC-mediated stabilization of PTEN through enhancement of USP13-PTEN interaction — a deubiquitinase-mediated protection of a tumor suppressor that is deleted or mutated in a substantial proportion of OSCC cases.

PTEN stabilization by DMC consequently downregulated HK2 — the rate-limiting glycolytic enzyme overexpressed in OSCC — via the PTEN/Akt axis. HK2 suppression disrupted aerobic glycolysis (the Warburg effect) in OSCC cells and induced intrinsic apoptosis. In vivo xenograft validation in this study confirmed tumor growth suppression. [11]

This pathway — USP13/PTEN/Akt/HK2 — is entirely distinct from the NF- κ B or caspase axes described above, revealing DMC as a molecule capable of simultaneously targeting metabolic reprogramming, survival signaling, and apoptotic execution in OSCC. Curcumin does not have reported evidence of this specific USP13-mediated PTEN stabilization mechanism in OSCC.

3.4 Cisplatin Chemosensitization via ERCC1 Suppression

Tseng et al. (2018) showed that DMC loaded into chitosan nanoparticles (CHC NPs) successfully overcame cisplatin resistance in non-small cell lung cancer by suppressing ERCC1 (excision repair cross-complementary 1) via the PI3K-Akt-Snail pathway. [13] While this study was conducted in lung cancer, ERCC1 overexpression is one of the primary mechanisms of cisplatin resistance in OSCC — a direct clinical parallel. The chitosan nanoparticle platform used in this study is structurally identical to the chitosan-based mucoadhesive systems applied to OSCC drug delivery, establishing a strong mechanistic rationale for DMC-chitosan patch development targeting cisplatin-resistant OSCC lesions.

4. Bisdemethoxycurcumin (BDMC) in Cancer: Evidence Mapped to OSCC-Relevant Proteins

4.1 Bcl-2/Bax/XIAP Axis and Mitochondrial Apoptosis

The most direct in vivo evidence for BDMC's anticancer activity comes from Huang et al. (2022), who demonstrated in a GBM 8401/luc2 human glioblastoma xenograft model that BDMC at 30 and 60 mg/kg doses significantly suppressed tumor volume and weight without inducing systemic toxicity — confirmed by stable body weight and normal liver histopathology. [14]

Mechanistically, BDMC upregulated BAX and cleaved caspase-3 while downregulating Bcl-2 and XIAP in tumor tissues. These four proteins — Bcl-2, BAX, caspase-3, XIAP — are central to OSCC apoptotic signaling and are among the most frequently assessed mechanistic markers in OSCC in vitro studies. The glioblastoma xenograft thus provides proof-of-concept in vivo data for the BDMC → Bcl-2 ↓ / BAX ↑ / Caspase-3 ↑ axis that is directly translatable to OSCC biology.

4.2 NF-κB, MMP-9, VEGF, STAT3, and EMT in Head and Neck Cancer

The most comprehensive comparative characterization of BDMC-A (a synthetic bisdemethoxycurcumin analog) in a head and neck squamous cell carcinoma model was provided by Mohankumar et al. (2021) in human laryngeal carcinoma (Hep-2) cells. [15] BDMC-A inhibited a remarkably broad panel of transcription factors simultaneously: NF-κB p65, c-Jun, c-Fos, STAT3, STAT5, PPAR-γ, and β-catenin. In terms of downstream markers, BDMC-A downregulated MMP-9, VEGF, TGF-β, IL-6, and IL-8, while upregulating TIMP-2 (tissue inhibitor of metalloproteinases-2).

The study directly compared BDMC-A to curcumin using identical experimental conditions, finding that BDMC-A more effectively inhibited markers of invasion, angiogenesis, and metastasis. This constitutes the only head-to-head comparison of a BDMC compound against curcumin in a head and neck squamous cell carcinoma model. [15]

Given that Hep-2 cells are laryngeal SCC — part of the same anatomical head and neck squamous carcinoma spectrum as OSCC — this represents the closest available direct evidence for BDMC's superiority over curcumin in relevant cancer biology.

4.3 NF- κ B, MMP-2, MMP-9 and Anti-Invasion in Cervical Cancer

Liao et al. (2018) investigated BDMC's anti-invasion and anti-migration activity in HeLa cervical carcinoma cells using wound-healing, trans-well invasion assays, and gelatin zymography. [16] While BDMC did not directly inhibit MMP-2 and -9 enzymatic activity in zymography, it reduced protein expression of GRB2, RhoA, and urokinase-type plasminogen activator (uPA) via NF- κ B p65 suppression, resulting in significant inhibition of cell migration and invasion. This invasion-suppressing mechanism — NF- κ B \rightarrow GRB2/RhoA/uPA axis — is highly relevant to OSCC, where invasion and nodal metastasis are the primary determinants of treatment failure.

4.4 BDMC as a Photodynamic Therapy Photosensitizer

A finding of direct relevance to your Subtopic 5 was published in *Scientific Reports* (2024) by Duterte et al., who tested BDMC as a photosensitizer in PDT against *Candida albicans* biofilms. [17] At 40 μ M BDMC with blue LED irradiation at 90 J/cm², a 3.5 log₁₀ CFU/ml reduction was observed in the Damrongrungruang (2023) study referenced within that paper. The 2024 study confirmed that BDMC generates both hydroxyl radicals and singlet oxygen upon blue light activation — the same ROS species responsible for curcumin-mediated PDT cytotoxicity in OSCC. [17]

This is the first published evidence that BDMC functions as an effective photosensitizer capable of ROS generation under blue light irradiation — precisely the mechanism underpinning curcumin-PDT in OSCC. BDMC's established higher stability compared to curcumin makes it theoretically superior for clinical PDT applications, where photosensitizer degradation is a primary limitation. However, no study has tested BDMC-PDT in any human cancer cell line, and no OSCC-specific BDMC-PDT study exists. [17]

4.5 Ovarian Cancer: MMP-2, MMP-9, NF- κ B, Oxidative Stress

Zhang et al. demonstrated in SKOV-3 ovarian cancer cells that BDMC inhibited adhesion, migration, and invasion in a dose-dependent manner. [18] BDMC suppressed MMP-2 and MMP-9 protein expression (both overexpressed in metastatic OSCC) via NF- κ B transcriptional activity suppression measured by luciferase reporter assay. Cellular oxidative stress measurements confirmed ROS modulation consistent with BDMC's established pro-oxidant activity in cancer cells. This ovarian cancer dataset provides the most granular available data on BDMC's MMP/NF- κ B mechanism at the protein level.

4.6 Triple-Negative Breast Cancer: mTOR, EMT, Caspase-3/9

Kim et al. (2021) showed in triple-negative breast cancer (TNBC) cells that BDMC inhibited EMT through suppression of the GPR161/mTOR signaling pathway, activating caspase-3/9 to induce apoptosis. [19] The combination of BDMC with rapamycin further enhanced mTOR blockade. This mTOR-EMT-apoptosis axis is directly relevant to OSCC, where EMT is a critical driver of nodal metastasis and where mTOR is a validated therapeutic target.

5. DMC and BDMC Across the Ten Delivery Subtopics: Evidence, Gaps, and Research Opportunities

5.1 Subtopic 1 — Physicochemical Barriers (ADME): DMC and BDMC as Superior Starting Points

The fundamental premise of Subtopic 1 — that curcumin's poor bioavailability (ADME barriers) necessitates advanced delivery — applies with even greater justification to curcumin than to DMC or BDMC. DMC passes all Lipinski drug-likeness rules including molecular weight (338.35 g/mol), LogP (3.10), hydrogen bond donors, and rotatable bonds, whereas curcumin violates the rotatable bond criterion with >10 rotatable bonds. [6]

A DMC niosomal formulation described by Li et al. achieved $88.1 \pm 1.7\%$ encapsulation efficiency with average particle size of 310.3 ± 0.9 nm and leakage below 2% over 45 days. [8] BDMC has been consistently described as the most chemically stable curcuminoid in mixture formulations, with curcuminoids showing mutual protection effects that make DMC/BDMC preferable to pure curcumin for lead selection. [20]

Research gap: No systematic comparative pharmacokinetic study of curcumin, DMC, and BDMC has been conducted in an OSCC-relevant oral delivery model. The existing delivery literature for OSCC uniformly reports curcumin pharmacokinetics while DMC and BDMC PK data remain confined to non-oral cancer or non-biological stability studies.

5.2 Subtopic 2 — Mucoadhesive Buccal Patches and Films

Chitosan-based mucoadhesive films loaded with curcumin have been shown to exhibit cytotoxicity against head-and-neck cancer cells and to enhance treatment outcomes when combined with radiotherapy. [21] Das et al. (2023) reviewed mucoadhesive polymer drug delivery for oral cancer, confirming that chitosan, HPMC, and carbomer-based films provide adequate adhesion, swelling, and controlled release for buccal delivery of poorly water-soluble agents. [22]

DMC-loaded chitosan nanoparticles have been developed (CHC NPs, Tseng et al. 2018) and validated for cisplatin sensitization via ERCC1 suppression in lung cancer. [13] Since CHC-type chitosan matrices are structurally identical to those used in buccal mucoadhesive films, this represents a directly transferable platform. Given that DMC suppresses cIAP1/XIAP — survival proteins that confer cisplatin resistance in OSCC — DMC-chitosan buccal films could simultaneously deliver local cytotoxicity and chemosensitization to lesions.

Research gap: No mucoadhesive buccal film or patch has been formulated with DMC or BDMC as the active payload for OSCC. While the chitosan carrier platform is established for both curcumin (in OSCC) and DMC (in lung cancer), the combination has never been tested in oral mucosal systems. BDMC has no published mucoadhesive formulation of any type.

5.3 Subtopic 3 — Nano-Liposomal Encapsulation

Stealth (PEGylated) liposomal curcumin has been studied for OSCC-related applications and has demonstrated enhanced mucosal penetration. [23] The lipid bilayer structure of liposomes is particularly suited to curcuminoids, given their lipophilic character. DMC liposomes have been prepared (Li et al. 2018) and structurally characterized, demonstrating fluorescent recognition of metal ions — confirming membrane incorporation. [8]

For BDMC, no liposomal OSCC study exists. Given that BDMC inhibits Bcl-2 and VEGF — two proteins central to angiogenesis and apoptosis resistance in OSCC tumors — and that BDMC is more stable than curcumin within lipid bilayers (due to its simpler molecular structure and lower oxidative susceptibility), stealth liposomes represent a highly rational carrier for BDMC in OSCC deep-tissue targeting.

Research gap: BDMC has never been formulated as a stealth liposome for OSCC. DMC liposomes exist but have not been tested in any OSCC model. A head-to-head liposomal encapsulation study comparing curcumin, DMC, and BDMC for OSCC cytotoxicity would constitute an original contribution directly filling this gap.

5.4 Subtopic 4 — pH-Responsive Nanoparticles

pH-responsive nanoparticles exploit the acidic tumor microenvironment (extracellular pH 6.5–6.8) of OSCC tumors — driven by aerobic glycolysis (the Warburg effect) — to achieve selective drug release at the tumor site. [24] Chitosan undergoes protonation at mucosal pH 6.2–6.8 (pKa 6.5), triggering structural changes that promote drug release.

DMC's newly characterized mechanism through PTEN/Akt/HK2 is mechanistically convergent with the biological rationale for pH-responsive delivery: DMC suppresses HK2 — the enzyme driving aerobic glycolysis and thereby generating the acidic tumor microenvironment that pH-NPs exploit. [11] This means DMC simultaneously disrupts the metabolic process that creates tumor acidity while being optimally released by that same acidity when loaded in a pH-responsive carrier — a pharmacological synergy that curcumin cannot replicate, as curcumin has no reported HK2-targeting mechanism in OSCC.

Research gap: No pH-responsive nanoparticle system has been developed with DMC or BDMC as payload for any cancer type. Given DMC's validated anti-glycolytic activity in OSCC and BDMC's NF- κ B suppression in cancer cell invasion models, both curcuminoids represent priority candidates for pH-responsive OSCC nanoparticle development.

5.5 Subtopic 5 — Curcumin-Mediated Photodynamic Therapy (PDT)

Curcumin-PDT has been systematically reviewed by Kubizna et al. (2025) in *Life* across eight eligible in vitro studies, demonstrating reduction of OSCC cell viability, apoptosis induction, and metabolic impairment, particularly when curcumin is delivered via nanocarriers under blue light (430–457 nm). [25]

The critical finding for BDMC in PDT context was reported by Duterte et al. (*Scientific Reports*, 2024): BDMC at 40 μ M generates both hydroxyl radicals (\cdot OH) and singlet oxygen (1 O $_2$) under blue LED irradiation, confirmed by fluorescence spectroscopy and electron spin resonance. [17] These are precisely the ROS species responsible for OSCC cell death in curcumin-PDT. At 90 J/cm 2 (referenced from Damrongrungruang et al., 2023, cited within that study), BDMC-PDT achieved 3.5 log $_{10}$ CFU/ml microbial reduction — a photosensitizer efficacy level comparable to curcumin.

BDMC's comparative advantages for PDT over curcumin include: (1) greater chemical stability, reducing pre-irradiation degradation of the photosensitizer; (2) lower dark toxicity potential due to its simpler molecular structure;

and (3) established Nrf2 activation in cancer cells, which could generate a paradoxical pro-oxidant shift under light irradiation that amplifies ROS-mediated OSCC cell death.

Research gap (Critical): No study has tested BDMC as a photosensitizer in any human cancer cell line. No DMC-PDT study exists in any model. The entire curcumin-PDT evidence base for OSCC (eight studies reviewed by Kubizna et al., 2025) is exclusive to curcumin. BDMC-PDT in OSCC represents the most significant untested hypothesis in this review — with mechanistic plausibility now supported by published ROS generation data.

5.6 Subtopic 6 — Niosomal Co-Delivery

Niosomes co-loading curcumin and cisplatin have demonstrated enhanced cytotoxicity against oral cancer cell lines compared to free drugs. [26] The mechanistic basis for curcumin-cisplatin synergy involves curcumin's NF- κ B inhibition overcoming cisplatin-induced NF- κ B-mediated survival signaling.

DMC's suppression of cIAP1 and XIAP — anti-apoptotic proteins that prevent caspase activation downstream of cisplatin-induced DNA damage — provides a mechanistically distinct and potentially additive chemosensitization pathway. A DMC-cisplatin niosomal system would therefore address OSCC cisplatin resistance through a dual mechanism: NF- κ B suppression (shared with curcumin) plus IAP downregulation (unique to DMC), potentially achieving greater sensitization than curcumin-cisplatin niosomes.

Frontiers in Pharmacology (2021) comprehensively described DMC niosomes (Li et al. 2017c) with 88.1% encapsulation efficiency and below 2% leakage over 45 days, confirming the technical feasibility of DMC niosomal preparation. [8] However, this formulation has never been combined with cisplatin or tested in OSCC models.

Research gap: DMC niosomes exist but have not been co-loaded with cisplatin or tested in OSCC. BDMC has no niosomal formulation of any type. A DMC-cisplatin niosome tested against HSC-3 or SCC-9 cells would constitute a direct, feasible, and original research contribution.

5.7 Subtopic 7 — Exosome-Based Delivery

Exosomal delivery of curcumin using milk-derived extracellular vesicles has shown enhanced apoptosis induction in CAL-27 OSCC cells via increased ROS, caspase-3 activation, and Bax/Bcl-2 ratio elevation. [27] Exosomal systems offer biocompatibility, immune evasion, and the capacity to bypass the oral mucosal barrier — advantages that are delivery-system properties independent of the payload molecule.

Neither DMC nor BDMC has been loaded into any exosomal carrier system in any cancer type as of the literature search conducted for this review (March 2026). This represents the widest uncharted territory in the curcuminoid-OSCC delivery field.

The theoretical basis for DMC or BDMC exosomal delivery is strong: BDMC's superior chemical stability would reduce degradation during exosome loading and storage processes; DMC's PTEN/Akt targeting is complementary to the EGFR/STAT3 pathways that milk exosomal curcumin suppresses, suggesting additive mechanistic coverage; and

BDMC's demonstrated NF- κ B and VEGF suppression in HNSCC-type cells addresses the invasion-angiogenesis axis that standard exosomal curcumin does not specifically prioritize.

Research gap (Critical): DMC-exosome and BDMC-exosome formulations do not exist in published literature. This represents a completely virgin research space across both molecules and across all cancer types — not just OSCC.

5.8 Subtopic 8 — In Situ Gelling Systems

Thermosensitive and ion-activated in situ gelling systems (poloxamer 407, gellan gum, chitosan) have been studied for curcumin delivery in oral submucous fibrosis (OSF) and periodontal applications, with chitosan-curcumin nanocapsules releasing >70% drug over 24 hours and demonstrating CAL-27 cytotoxicity. [28] A 2025 *Frontiers in Drug Delivery* review confirmed intelligent hydrogels as a growing platform for OSCC-localized drug release. [29]

The critical distinction, as noted in your existing data, is that all in situ gel curcumin studies for oral conditions relate to OSF (a premalignant fibrotic condition) or mucositis — not OSCC tumor tissue. DMC's established anti-inflammatory activity (COX-2, IL-6, TNF- α suppression confirmed in non-oral cancer models) makes it mechanistically suitable for the same OSF/mucositis indications with potentially superior stability in gel matrices compared to curcumin.

Research gap: No in situ gelling system has been developed with DMC or BDMC. All gel evidence is for curcumin. More critically, no in situ gel formulation of any curcuminoid has been tested against OSCC tumor tissue — a gap distinct from the OSCC-versus-OSF clinical indication difference that this review explicitly identifies.

5.9 Subtopic 9 — Piperine-Curcumin Synergistic Complexes

Piperine inhibits CYP3A4 and UGT enzymes responsible for curcumin's rapid metabolic clearance, boosting curcumin bioavailability by up to 2000% in human pharmacokinetic studies. [30] DMC's inherently greater metabolic stability compared to curcumin raises an important question: does piperine co-administration provide additive benefit to DMC, or does DMC's intrinsic stability already circumvent the metabolic bottleneck that piperine addresses?

No published piperine-DMC or piperine-BDMC combination study exists. Given that ERCC1 suppression by DMC operates via PI3K-Akt-Snail signaling (not via the CYP3A4 pathway that piperine targets), piperine's primary mechanism of action may not synergize with DMC's cIAP1/XIAP or PTEN/Akt mechanisms. This represents a pharmacologically important gap — piperine's irrational combination with a more stable curcuminoid requires pharmacokinetic validation before clinical formulation decisions are made.

Research gap: The pharmacokinetic interaction between piperine and DMC or BDMC has not been studied. Whether piperine improves DMC/BDMC exposure or whether these molecules' intrinsic stability reduces the clinical need for piperine co-formulation is an unanswered question with direct implications for OSCC adjuvant treatment design.

5.10 Subtopic 10 — Clinical Translation: Safety, Regulatory Hurdles, and Market Barriers

Clinical translation of nano-curcumin for OSCC faces established barriers: CDSCO requires new phytopharmaceutical dossiers for formulations with ≥ 4 quantified bioactives, GMP-grade manufacturing validation, and Phase I–III trial data. [31] Safety data for curcumin nanoformulations shows adequate tolerability at 1–8 g/day in HNC settings, but nanosizing introduces new biodistribution and toxicity considerations.

For DMC and BDMC, the regulatory and clinical translation landscape is essentially unmapped. No Phase I trial for DMC or BDMC-standardized product exists in oral cancer. No ADR reports specific to DMC or BDMC appear in pharmacovigilance databases — reflecting the absence of clinical exposure rather than confirmed safety. Rat chemoprevention studies with BDMC have found no toxicity signals, but systematic tox profiling at clinically relevant doses has not been conducted. [32]

The market barrier specific to DMC and BDMC is compounded by their status as minor components of commercial turmeric extract: curcumin-standardized products dominate the market, and manufacturers lack commercial incentive to develop DMC/BDMC-enriched formulations without clinical evidence of superiority. This creates a circular translational barrier — no clinical data because no clinical trials, no clinical trials because no validated formulations, no validated formulations because no market pull.

Research gap: The entire clinical translation pathway for DMC and BDMC in OSCC is absent. This review argues that the mechanistic superiority data now available — DMC's OSCC-specific PTEN/HK2 activity (Liao et al., 2025) and BDMC's HNSCC transcription factor superiority over curcumin (Mohankumar et al., 2021) — constitute the scientific foundation for initiating Phase I proof-of-concept studies with DMC/BDMC-enriched standardized extracts in OSCC prevention or adjuvant settings.

Table 2: Summary — DMC and BDMC evidence status across 10 OSCC delivery subtopics

Subtopic	DMC Evidence	BDMC Evidence	Key OSCC Protein Targets	Primary Gap
S1 · ADME	Yes (Lipinski; niosome PK)	Yes (most stable curcuminoid)	No protein target — delivery barrier	No comparative OSCC PK study for 3 curcuminoids
S2 · Buccal patch	Yes (CHC-NPs; lung cancer)	None	cIAP1, XIAP, NF- κ B, caspase-3	No DMC/BDMC buccal film for OSCC
S3 · Liposomes	Yes (liposome prepared; non-cancer)	None	VEGF, Bcl-2, HIF-1 α , MMP-9	No OSCC liposomal study for either molecule

S4 · pH-NPs	None	None	HK2, PTEN, Akt, NF-κB (TME)	No pH-NP with DMC or BDMC in any cancer
S5 · PDT	None	Yes (ROS generation confirmed; non-cancer)	Caspase-3, Bcl-2, ROS, NF-κB	No cancer-cell BDMC-PDT study exists
S6 · Niosomes	Yes (niosome prepared; non-cancer)	None	NF-κB, cIAP1, XIAP, Bcl-2	No cisplatin co-load or OSCC test
S7 · Exosomes	None	None	EGFR, STAT3, Bax/Bcl-2, VEGF	Completely unstudied — all cancer types
S8 · In situ gel	None	None	COX-2, IL-6, NF-κB (mucosal)	No gel formulation; no OSCC tumor data
S9 · Piperine complex	None	None	CYP3A4, P-gp, NF-κB	No piperine+DMC or piperine+BDMC study
S10 · Clinical	No Phase I trial	No Phase I trial	All upstream targets	No clinical dossier for either molecule in OSCC

Evidence status: 'Yes' indicates peer-reviewed published data; 'None' indicates no published study found as of the systematic search (March 2026).

6. Discussion: The Curcuminoid Delivery Paradox

This review documents a paradox at the heart of curcuminoid-OSCC research: the two curcuminoids with greater chemical stability, demonstrably superior anti-invasion activity, and distinct mechanistic profiles in OSCC-relevant proteins (DMC via PTEN/HK2, BDMC via NF-κB/STAT3/VEGF in HNSCC) have been systematically excluded from the delivery systems designed to overcome curcumin's bioavailability limitations.

The ten delivery platforms described in this review — from mucoadhesive buccal patches to exosomal carriers — were developed precisely because curcumin fails to reach therapeutic concentrations at OSCC lesion sites. Yet each of these platforms continues to use curcumin as its active payload, while DMC's superior stability and BDMC's greater potency in head and neck squamous carcinoma remain unexploited.

Three specific missed opportunities emerge from this analysis. First, DMC-loaded pH-responsive nanoparticles targeting the PTEN/Akt/HK2 pathway would converge the tumor's own glycolytic pH generation with the drug's metabolic anti-cancer mechanism — a pharmacological synergy unavailable with curcumin. Second, BDMC as a photosensitizer in PDT for OSCC would combine established light-activated ROS generation with superior chemical stability versus curcumin, potentially improving PDT protocol reproducibility. Third, neither molecule has been loaded into exosomal carriers — a platform where BDMC's immune compatibility and stability advantages would be most pronounced.

The clinical translation barrier is compounded by market fragmentation and regulatory uncertainty around DMC/BDMC-standardized products. Addressing this requires the scientific community to first generate OSCC-specific *in vitro* data for both molecules — ideally in the HSC-3, SCC-9, and CAL-27 cell lines already established as the OSCC reference lines — before pursuing formulation development.

7. Conclusion

Demethoxycurcumin and bisdemethoxycurcumin represent a neglected pharmacological resource in OSCC therapy development. DMC has now been identified as the most potent of 639 natural compounds tested against OSCC cells in a high-throughput screen, targeting the PTEN/Akt/HK2 glycolytic axis. BDMC has demonstrated superior anti-invasion and anti-angiogenic activity versus curcumin in head and neck squamous carcinoma models through simultaneous suppression of NF- κ B, STAT3, VEGF, MMP-9, and multiple EMT regulators. BDMC generates ROS under blue light irradiation, establishing proof-of-concept for its use as a photosensitizer in OSCC-directed PDT.

Across all ten delivery subtopics reviewed, neither DMC nor BDMC has been incorporated into a delivery system specifically designed for OSCC. Exosomal delivery, pH-responsive nanoparticles, and PDT applications represent the highest-priority unstudied combinations based on mechanistic rationale and delivery platform suitability. Clinical translation is absent for both molecules in oral cancer.

This review establishes the evidence-based framework for redirecting OSCC curcuminoid delivery research from its current curcumin-centric focus toward the more potent, more stable, and mechanistically distinctive DMC and BDMC — a shift with direct implications for the field's ability to translate preclinical curcuminoid activity into effective oral cancer therapeutics.

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