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Demothoxycurcumin as a curcumin analogue with anticancer, antimicrobial, anti-inflammatory, and neuroprotective activities: Micro and nanosystems

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ABSTRACT

Numerous therapeutic benefits have been associated with polyphenolic compounds possessing multiple hydroxyl functional groups. In the realm of traditional medicine, curcuminoids extracted from the rhizomes of the turmeric (*Curcuma longa* Linn) plant, specifically curcumin, demethoxycurcumin, and bisdemethoxycurcumin, have been recognized for their potential in addressing a wide range of health issues. These issues encompass injuries, infections, stress, cancer, skin ailments, and neurological disorders. Of particular interest, demethoxycurcumin has demonstrated a remarkable safety profile even at high doses. It has exhibited promising therapeutic properties, including its potential as an antitumor agent and its effectiveness in combating microbial infections. In the case of its antibacterial mechanism, demethoxycurcumin has been found to disrupt the transpeptidase, thus impeding the synthesis of glycopeptides in the bacterial cell wall. Demethoxycurcumin, akin to its curcumin and bisdemethoxycurcumin counterparts, can modulate cell proliferation and inflammatory signaling pathways. However, it is essential to acknowledge that specific clinical challenges are associated with unveiling the full scope of its therapeutic activities and optimizing its formulation on a micro and nanoscale. These challenges and potential solutions are further explored in this concise review.

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1.Introduction

There are numerous health benefits for polyphenolic compounds with multiple hydroxyl functional groups and the ability to reduce reactive oxygen species (ROS) [1-4]. According to chemical structures, there are four main polyphenols groups: phenolic acids, lignans, flavanoids and stilbenes [5-7]. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are known as curcuminoids of *Curcuma longa* Linn. (Turmeric) root extracts by values of about 77%, 17% and 3%, respectively [8]. In contrast to curcumin, demethoxycurcumin or monodemethoxycurcumin ($C_{20}H_{18}O_5$) does not have the methoxy group on the benzene ring (Figure 1), which results in appropriate chemical stability at acidic pH [9]. Vasodilatory, antihypertensive, antifungal, antibacterial, antimalarial, anti-inflammatory, and neuroprotective properties have been indicated as the main therapeutic activities of demethoxycurcumin [10-12]. Furthermore, this metabolite can inhibit nitric oxide (NO) and scavenge free radicals from oxidative stress [13]. However, demethoxycurcumin, similar to other polyphenolic compounds, can be formulated by suitable micro or nanomaterials to overcome clinical hindrances including short circulation time and stability [14-18]. Various nanomaterilas with unique physicochemical features can be regarded as promising nanocarriers for delvery of synthetic and organic therapeutic agents [19, 20]. Therefore, in this study, clinical limitations for the formulation of demethoxycurcumin have been discussed by presenting novel micro and nanoformulations with adequate efficacy in physiological conditions.

2. Anticancer activity

In a comparative study, treatment of mice with orthotopic glioblastoma xenografts at a concentration of 20 mg/kg demethoxycurcumin illustrated lower tumor inhibitory effects 14 days compared to its derivative 1-[4-Hydroxy-3-(pyrrolidin-1-ylmethyl)

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phenyl]-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione, named BMC-BH at the same concentration. BMC-BH hindered the expression of Ki67, p-Akt (Phosphorylated protein kinase B), p-mTOR (Phosphorylated mammalian target of rapamycin), and augmented the incidence of TUNEL (Terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling)-positive cells [21]. Two main anticancer mechanisms involving inhibiting the proliferation of oral squamous cell carcinoma by inducing G2/M-phase arrest and cell apoptosis have been indicated for demethoxycurcumin. Furthermore, this metabolite activated c-Jun N-terminal kinase (JNK)1/2 and p38 mitogen-activated protein kinase (MAPK) in oral squamous cell carcinoma. Other main molecular mechanisms of demethoxycurcumin inhibiting the growth of oral squamous cell carcinoma have been illustrated in Figure 2 [22]. Glioblastoma multiforme or glioblastoma, a grade IV astrocytoma, is the primary aggressive brain malignancy with poor therapeutic outcomes [23]. In a comparative study, four curcumin derivatives with different methoxy groups have been employed to treat human LN229 and GBM8401 glioma cells. This study exhibited that demethoxycurcumin, similar to curcumin, dimethoxycurcumin, and bisdemethoxycurcumin can induce apoptosis, G2/M arrest, ROS generation, and sub-G1 phase in these glioma cells [24]. Three main curcuminoids involving bisdemethoxycurcumin, curcumin, and demethoxycurcumin, isolated from turmeric by a mixture of chloroform: methanol: water hindered the proliferation of T98G glioblastoma, A549 human lung cancer, and HT29 colon cancer cell lines in a dose-dependent way [25]. Some anticancer drugs, such as 6-Mercaptopurine (6-MP),have limited bioavailability in physiological conditions. Biocompatible and biodegradable natural compounds such as turmeric oil may be desirable for encapsulation and loading these drugs in micro or nanoscale. Turmeric oil (15%)-based self-nano emulsifying drug delivery system (SNEDDS) has been employed to increase the bioavailability of 6-MP in a size range of 425.7–303.6 nm and polydispersity index (PDI) of 0.42–0.69 (Figure 3a). This nanoformulation exhibited a significant reduction in the numbers of the HepG2 cells (human liver cancer cell line) in the G1/G0 phase (Figure 3b and c) [26]. Demethoxycurcumin can induce DNA damage and condensation in NCI-H460 cell line (a large cell lung cancer). In addition, p-H2A.X (phospho Ser140) and phosphorylated p53 (tumor suppressor protein) were activated in NCI-H460 cells under effect of demethoxycurcumin [27].

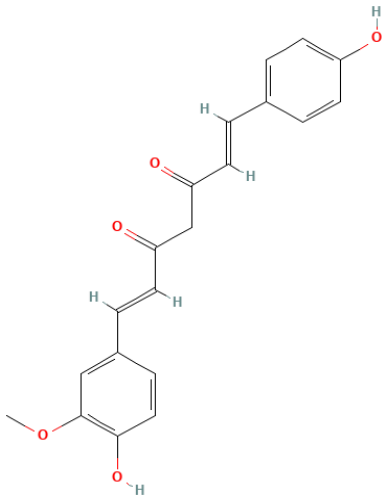

Fig. 1. Chemical structure of demethoxycurcumin (Source: PubChem).

3. Antimicrobial activity

Similar to other medicinal plant extrcts [28], turmeric extract can be used in a time-consuming and eco-friendly way to synthesize or modify organic and inorganic nanomaterials such as carbon quantum dots [29-31]. Ethanol extract of turmeric powder was employed to fabricate carbon dots powder at 60 °C with a mean diameter of 10.7 nm. These carbon dots exhibited antibacterial effects of *E. coli and S. aureus* by producing ROS resulting from a photodynamic mechanism under a 405 nm (20 mW/cm^2) light source [32]. In a comparative study, demethoxycurcumin showed more antibacterial activity against *Escherichia coli* than *Staphylococcus aureus* and *Shigella dysenteriae*. Depending on the difference in the cell wall composition between bacterial species, demethoxycurcumin hindered the exponential phase of the growth of *S. aureus* and *E. coli*; however, this metabolite hindered the lag phase of *S. dysenteriae*. The probable antibacterial mechanism has been found as a combination of demethoxycurcumin with transpeptidase to block the synthesis of glycopeptides in the bacterial cell wall [33].

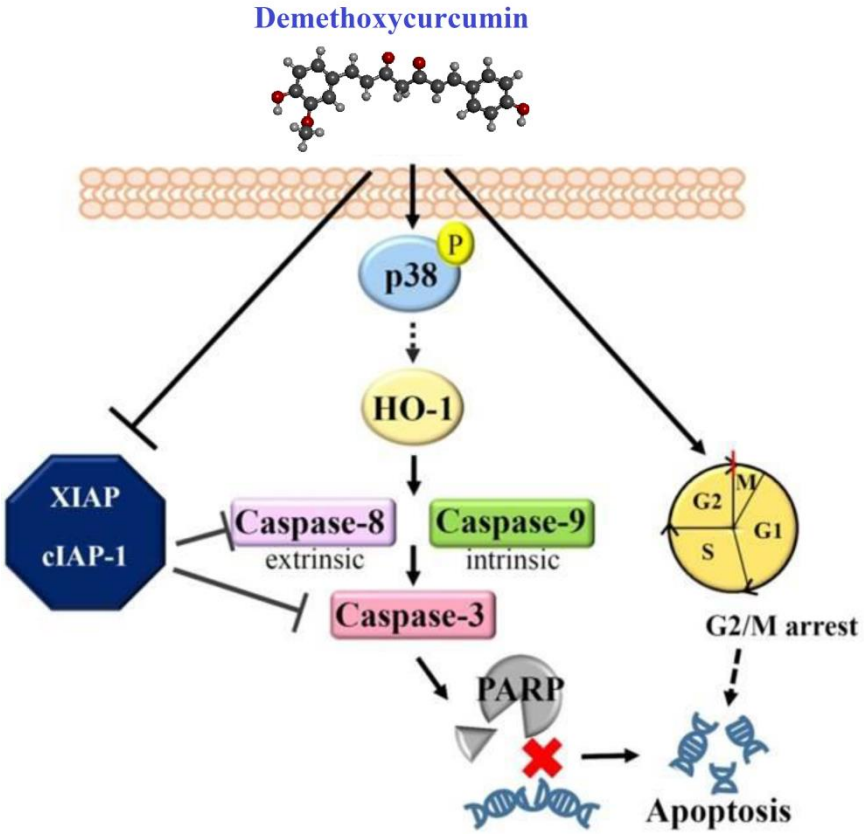

Fig. 2. The central molecular mechanism of demethoxycurcumin to inhibit the growth of oral squamous cell carcinoma; the cellular inhibitor of apoptosis 1 (cIAP1)/X-chromosome-linked IAP (XIAP); poly(ADP-ribose) polymerase (PARP) (Adapted and modified from [22]).

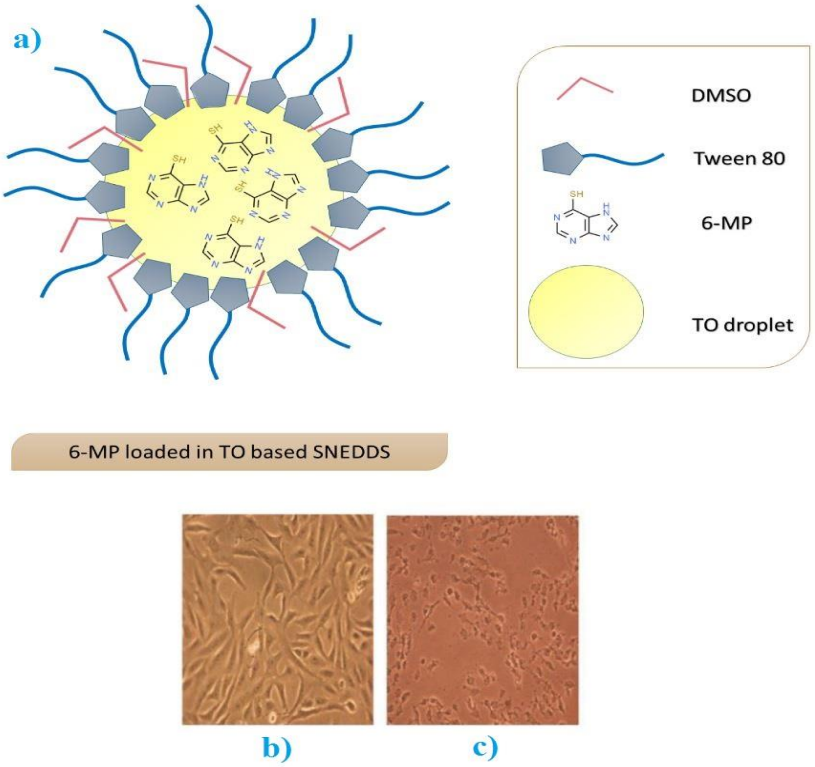

Fig. 3. a) Scheme image of loading 6-MP by turmeric oil-based SNEDDS, b) control, and c) treated HepG2 cells by the SNEDDS at a concentration of 12.5 µg/mL (adopted and modified from [26]).

Similar to other curcuminoids, a variety of micro- and nanoformulations, including microparticles, nanoparticles, nanocrystals, nanocapsules, nano polymers, and lipid nanoparticles, may be employed to increase the bioavailability and antimicrobial activity of demethoxycurcumin [34]. Liposomes and nanoliposomes can be considered as promising drug delivery systems for loading and encapsulating of hydrophobic and hydrophilic therapeutic agents [35, 36]. Loading turmeric extract by nanoliposomes in an average diameter of 92 nm, PDI of 0.40, and Zeta potential of −10.1 mV showed minimum bactericidal concentration (MBC) values of 0.58 and 0.07 mg/mL compared to pure turmeric extract with values of 1.17 and 0.58 mg/mL against *S. aureus* and *E. coli*, respectively [37].

4. Anti-inflammatory activity

Demethoxycurcumin compound has remarkably inhibited tumor necrosis factor-α (TNF-α) and nitric oxide (NO). This metabolite can suppress the production of NO induced via lipopolysaccharide (LPS) in N9 microglial cells. In addition, the reduction of LPS-induced interleukin-1β (IL-1β) and TNF-α expression and blockage of the IκBα (inhibitor of nuclear factor kappa B) phosphorylation and the phosphorylation of MAPKs may be the result from anti-inflammatory effect of demethoxycurcumin [13]. Lung inflammation may be caused by a response to the external airborne toxic stimuli and substantial cell injury [38]. In addition, in severe acute respiratory syndrome coronavirus (SARS-CoV), out-of-control response by the immune system leads to a cytokine storm [39]. As a nanoformulation, a high-energy microfluidization method has been employed to prepare nanoemulsion of turmeric in edible sesame oil in a 200–250 nm size range. These nanoemulsions significantly reduced inflammatory cytokine levels, including interleukin-4 (IL-4), IL-13, and IL-6, and neutrophils in bronchoalveolar lavage fluids [40].

5. Neuroprotective activity

Treatment of transgenic Alzheimer's mice (Tg2576) by the standardized turmeric extract exhibited hindering microglial inflammation and Tau phosphorylation [41]. Oxidative stress and mitochondrial dysfunction can result in dopaminergic neuronal death in Parkinson's disease (PD) [42, 43]. Demethoxycurcumin pretreatment in a dose-dependent way decreased rotenone-induced cell death in SH-SY5Y cells by reducing oxidative stress and mitochondrial dysfunction [44]. In another study, oral administration of demethoxycurcumin towards rotenone-induced PD in rats showed reduced oxidative stress, neurochemical deficits, motor dysfunctions, and expressions of inflammatory markers [45]. As mentioned in the above section, LPS can promote the production of TNF-α and NO in highly aggressively proliferating immortalized (HAPI) microglial cells. O-demethyldemethoxycurcumin and di-O-demethylcurcumin exhibited more ability to inhibit the mRNA expression level of inducible NO synthase than curcumin and demethoxycurcumin [46]. In a comparative study, neuroprotective effects of curcumin, demethoxycurcumin, and bisdemethoxycurcumin have been evaluated against lead-induced neurotoxicity in male Wistar rats for 5 days of treatment. Demethoxycurcumin and curcumin caused less oxidized proteins and higher glutathione in the hippocampus of the animal model compared to bisdemethoxycurcumin and the control group [47].

6. Conclusions

Demethoxycurcumin compound activates JNK1/2 and p38 MAPK in oral squamous cell carcinoma. This polyphenolic compound, similar to other curcuminoids, including curcumin, dimethoxycurcumin, and bisdemethoxycurcumin, can induce apoptosis, G2/M arrest, ROS generation, and sub-G1 phase in human glioma cells. Furthermore, the demethoxycurcumin isolated from turmeric blocked the proliferation of T98G glioblastoma, A549 human lung cancer, and HT29 colon cancer cell lines in a dose-dependent way. Demethoxycurcumin can induce DNA damage, and activate p-H2A.X and phosphorylated p53 in NCI-H460 cells. The antibacterial mechanism of demethoxycurcumin may be hindering the transpeptidase to block the synthesis of glycopeptides in the bacterial cell wall. In addition,

Depending on the difference in the cell wall composition between bacterial species, demethoxycurcumin can inhibit the lag or exponential phase of bacterial growth. Striking inhibitory impact on TNF-α and NO has been reported for demethoxycurcumin compound as the main anti-inflammatory activity. Demethoxycurcumin pretreatment in a dose-dependent manner can reduce oxidative stress and mitochondrial dysfunction. Similar to other curcuminoids, a variety of micro- and nano-formulations, including microparticles, nanoparticles, nanocrystals, nanocapsules, lipid nanoparticles, and nanopolymers, may be utilized to increase the bioavailability and therapeutic activity of demethoxycurcumin. Although there are many studies about nanoformulations of curcumin or turmeric extract with promising health benefits, however, pure demethoxycrucumin has not been formulated in biocompatible nanomaterials.

Study Highlights

- Demethoxycurcumin compound activates JNK1/2 and p38 MAPK in oral squamous cell carcinoma.
- Demethoxycurcumin blocked the proliferation of T98G glioblastoma, A549 human lung cancer, and HT29 colon cancer cell lines.
- This metabolite induces DNA damage and, activates p-H2A.X and phosphorylated p53 in NCI-H460 cells.
- Demethoxycurcumin hinders the transpeptidase to block the synthesis of glycopeptides in the bacterial cell wall.
- Nano-formulations, such as lipid nanoparticles and nanopolymers can be employed to augment the bioavailability and therapeutic activity of demethoxycurcumin.

Abbreviations

cIAP1: Cellular inhibitor of apoptosis 1
IL-1β: Interleukin-1β
IL-4: Interleukin-4
JNK: c-Jun N-terminal kinase
LPS: Lipopolysaccharide
MAPK: Mitogen-activated protein kinase
MAPKs: Mitogen-activated protein kinases
NO: Nitric oxide
P-Akt: Phosphorylated protein kinase B
PARP: Poly(ADP-ribose) polymerase
PD: Parkinson's disease
PDI: Polydispersity index
P-mTOR: Phosphorylated mammalian target of rapamycin
ROS: Reactive oxygen species
SARS-CoV: Severe acute respiratory syndrome coronavirus
TNF-α: Tumor necrosis factor-α
TUNEL: Terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling
XIAP: X-chromosome-linked IAP

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author contributions

All authors: conceptualization, writing the first draft, and revising the manuscript.

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