Micro Nano Bio Aspects

https://www.mnba-journal.com

Online ISSN: 2980-8081

Anticancer, antimicrobial, anti-inflammatory, and neuroprotective effects of bisdemethoxycurcumin: Micro and nano facets

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ARTICLE INFO

Review paper

Article history:
Received: 16 Sep 2023
Revised: 17 Oct 2023
Accepted: 19 Oct 2023
ePublished: 20 Oct 2023

Keywords:
Turmeric, Curcuminoids, Bisdemethoxycurcumin, Anti-acidogenic, Radioprotective, Nanoformulations

ABSTRACT

In recent years, various approved drugs have been developed deriving from natural sources with potential therapeutic applications. Among these natural metabolites, curcuminoids as phenolic compounds related to Turmeric have obtained great attention. Three main curcuminoids are bisdemethoxycurcumin, demethoxycurcumin, and curcumin with a variety of therapeutic potentials. These polyphenols exhibited numerous therapeutic activities involving anti-acidogenic, antioxidant, anti-inflammatory, anticancer, neuroprotective, antimicrobial, and radioprotective. Low bioavailability is the major limitation of these metabolites that can be ameliorated by novel biocompatible and bioavailable formulations. It must be noted that there are few investigations related to bisdemethoxycurcumin compared to curcumin and demethoxycurcumin, which we have discussed this metabolite in both micro and nanoformulations.

DOI: https://doi.org/10.22034/mnba.2023.416625.1046

Introduction

In recent years, comprehensive studies have exhibited therapeutic activities of curcuminoids involving anti-acidogenic, antioxidant, anti-inflammatory, anticancer, neuroprotective, antimicrobial, and radioprotective [1, 2]. Turmeric root extract as yellow power contains curcuminoids including bisdemethoxycurcumin (3-10%), demethoxycurcumin (17-20%), and curcumin (70-77%) [3, 4]. Although bisdemethoxycrucumin with a chemical formula of $C_{19}H_{16}O_4$ (Figure 1) has illustrated potential anti-inflammatory, anticancer, and antimicrobial effects, there are fewer studies about this metabolite compared to curcumin [5, 6]. It should be noted that nano approaches to formulate bisdemethoxycurcumin may be more promising compared to other approaches. Similar to curcumin and other polyphenols, numerous nanomaterials in zero, one, and two dimensions can be employed to deliver of this metabolite [7-9]. In this way, this review has tried to address recent advances and challenges related to new formulations of bisdemethoxycurcumin.

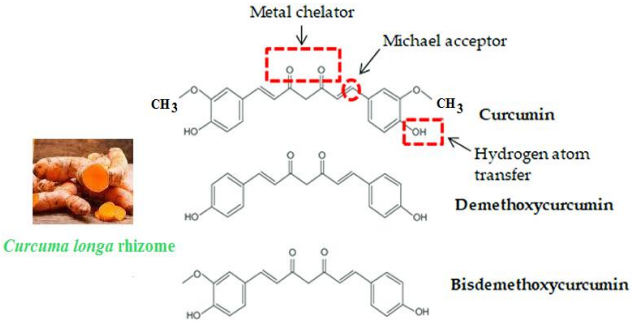

Fig. 1. Chemical structures of curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Adopted with modified from [10]).

Anticancer effect

As the main antitumor mechanisms, induction of apoptotic death and hindering of proliferation, growth, metastasis, migration, and invasion of tumor cells have been indicated for bisdemethoxycurcumin [11].

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Induction of apoptosis through the increase of Bcl-2-associated X (BAX; pro-apoptotic proteins), inactivation of Bcl-2 (B-cell lymphoma 2: anti-apoptotic protein), and cytochrome c release in human glioblastoma (GBM) 8401/luc2 cells can be led by bisdemethoxycurcumin treatment. In molecular mechanisms, in comparison to the control group, there was up-regulation of cleaved caspase-3 and BAX expression and down-regulation of the protein expressions of the X-linked inhibitor of apoptosis protein (XIAP) and Bcl-2 in the tumor tissues (Figure 2) [12].

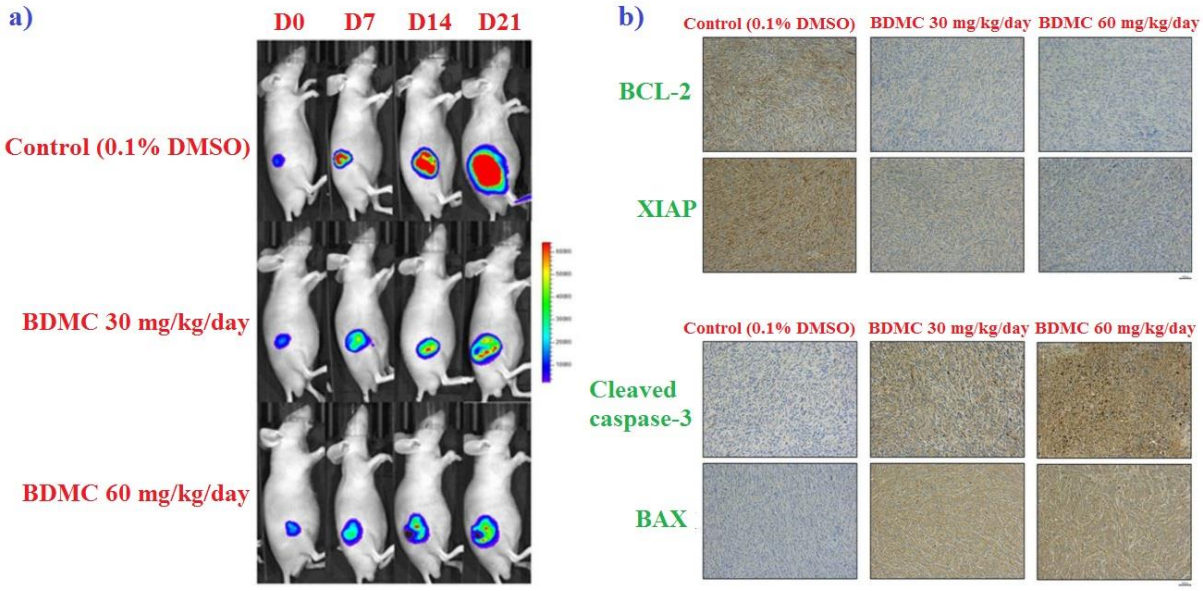

Fig. 2. a) Reduction of the living cell population within the tumor upon effect of bisdemethoxycurcumin (BDMC). b) The expression of apoptosis-related proteins in GBM 8401/luc2 cell xenografts was affected by BDMC [12].

In their research, Liao et al. (2018) explored the impact of bisdemethoxycurcumin on HeLa cervical cancer cells, highlighting its potential as an inhibitor of cancer cell migration and invasion through various molecular pathways [13]. They initiated the study by assessing the cytotoxicity of bisdemethoxycurcumin on HeLa cells and identified a non-lethal dose for further investigation. Notably, bisdemethoxycurcumin significantly hindered cell mobility and effectively reduced both cell migration and invasion *in vitro*. Molecular analysis unveiled significant alterations induced by bisdemethoxycurcumin. It downregulated key proteins associated with cancer metastasis, including GRB2 (Growth factor receptor-bound protein 2), MMP-2 (Matrix metalloproteinase-2), MMP-9, RAS, RhoA (Ras homolog family member A), SNAIL (Zinc finger protein SNAI1), N-cadherin, vimentin, β-catenin, uPA (Urokinase plasminogen activator), and ERK1/2 (Extracellular signal-regulated protein kinases 1 and 2). Interestingly, bisdemethoxycurcumin did not impact the gelatinase activity of MMP-2 and MMP-9. Importantly, bisdemethoxycurcumin induced a transition from mesenchymal to epithelial characteristics by increasing E-cadherin expression and decreasing N-cadherin. Furthermore, bisdemethoxycurcumin demonstrated the ability to suppress NF-κB (Nuclear factor-κB), a transcription factor closely tied to cell survival, proliferation, and metastasis. Intriguingly, it inhibited ERK1/2 while increasing phospho-ERK1/2, suggesting a potential involvement of ERK1/2 phosphorylation in bisdemethoxycurcumin-mediated effects [13].

Throughout the Ramezani research (2018), it becomes evident that bisdemethoxycurcumin possesses a multifaceted arsenal against cancer. Evidence suggests that bisdemethoxycurcumin can hinder the various stages of carcinogenesis, including tumor formation, promotion, and development. Like curcumin, bisdemethoxycurcumin demonstrates anti-tumor properties through the modulation of several critical molecular targets associated with cancer (see Figure 2). bisdemethoxycurcumin triggers apoptosis and affects the cell cycle, while also curbing cancer cell invasiveness and metastasis, which are advanced stages in cancer progression. Bisdemethoxycurcumin

exhibited promising anti-cancer properties by targeting multiple molecular pathways involved in cancer development and progression. These pathways include NF-κB, phosphatidylinositol 3‑kinase (PI3K)/protein kinase B (AKT), mitogen activated protein kinases (MAPK), apoptotic pathways, angiogenesis, and Wnt (Wingless-related integration site)/β-catenin. It's important to note that the specific pathways targeted by bisdemethoxycurcumin can vary depending on the type of cancer and the context of the research [11].

In another study, it was demonstrated that bisdemethoxycurcumin has a significant impact on cancer cell dynamics by halting cell cycle progression at the G1 phase, which disrupts uncontrolled cell proliferation. It targets key molecular components like MMPs, urokinase, and CD147, thereby inhibiting extracellular matrix degradation and tumor invasion. Moreover, it reduces oxidative stress levels, which is linked to its ability to hinder cancer cell invasion and metastasis, illustrating the connection between oxidative stress and MMP secretion. Bisdemethoxycurcumin's influence extends to the NF-κB pathway, a significant player in cancer progression. By effectively stifling NF-κB-driven transcriptional activity, bisdemethoxycurcumin strategically obstructs a critical pathway to tumor initiation and metastasis. This strategic move is further substantiated by the notable reduction in phosphorylation levels of key proteins, including p65 and IκB-α (IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha). This multifaceted approach showcases its potential as a cancer-fighting agent, offering hope for more effective cancer research and therapeutic interventions in the future [14].

Antimicrobial effect

In their 2020 research, Wang et al. investigated bisdemethoxycurcumin's antibacterial mechanism, primarily focusing on MRSA. They found that this polyphenolic compound disrupts bacterial cell walls, weakening their structural integrity and increasing permeability. Consequently, antibiotics can enter bacterial cells more effectively, improving their antibacterial action. Bisdemethoxycurcumin directly inhibits MRSA growth, acting as a bacteriostatic agent. It also reduces the expression of specific antibiotic-resistance genes in MRSA, such as mecA, blaZ, beta-lactam sensor-transducer blaR1, and mecR1. This downregulation counters MRSA's resistance mechanisms, making it more susceptible to antibiotic treatment. In summary, bisdemethoxycurcumin's antibacterial mechanism involves cell wall disruption, enhanced antibiotic permeability, growth inhibition of MRSA, and the suppression of antibiotic resistance genes. Bisdemethoxycurcumin inhibits the ATPase enzymes and increase the permeability of the bacterial membrane. Antibacterial mechanisms of bisdemethoxycurcumin against methicillin-resistant *Staphylococcus aureus* (MRSA) have been found to be reduction of the penicillin-binding protein 2a (PBP2a) and the *mec*A transcription gene. Growth of six strains of MRSA was inhibited at the minimal inhibitory concentration (MIC) of 7.8 ppm [15].

In a different study, researchers explored how bisdemethoxycurcumin, a derivative of curcumin, acts as an antibacterial agent against *Clostridium difficile*. This investigation unveiled several facets of its antibacterial mechanism. Bisdemethoxycurcumin inhibits the growth of *C. difficile*, which indicates one of its key functions is hindering bacterial replication and proliferation. Additionally, it disrupts the integrity of the bacterial cell membrane, making the bacterium more susceptible to external factors and other antibacterial agents. The study also highlighted bisdemethoxycurcumin's potential anti-toxin activity against *C. difficile*. This is particularly important because the toxins produced by this bacterium are responsible for its pathogenicity and the onset of disease symptoms. Bisdemethoxycurcumin's ability to counteract these toxins is a significant component of its antibacterial mechanism. Furthermore, bisdemethoxycurcumin was observed to influence the expression of specific genes in *C. difficile*. This modulation of gene expression may disrupt essential bacterial functions, further contributing to its antibacterial effect. Moreover, the study suggests that bisdemethoxycurcumin may synergize with antibiotics, potentially enhancing the overall antibacterial activity. Combining bisdemethoxycurcumin with antibiotics could lead to improved treatment outcomes in *C. difficile* infections[16]. In light of these findings, bisdemethoxycurcumin emerges as a promising natural antibacterial agent, especially when used alongside antibiotics. These insights offer potential strategies for addressing antibiotic-resistant bacterial infections.

Anti-inflammatory effect

Inflammation is a crucial response to various conditions in organisms, but excessive inflammation can lead to conditions like atherosclerosis, rheumatoid arthritis, and asthma. Pro-inflammatory cytokines play a significant role in the inflammatory process, including IL-1β (Interleukin 1 beta), IL-6, IL-13, and TNF-α (Tumor necrosis factor-α). IFN-γ, although known as a pro-inflammatory cytokine, has complex effects and can also have anti-inflammatory properties [17]. In another study, the authors investigated the anti-inflammatory effects of various curcumin analogs, including bisdemethoxycurcumin which indicated, that bisdemethoxycurcumin, along with other curcumin analogs, was evaluated for its ability to modulate anti-inflammatory responses. The results indicated that bisdemethoxycurcumin exhibited anti-inflammatory activity, but the extent of its effect differed from that of other analogs such as curcumin and bisdemethoxycurcumin. One notable finding was that the anti-inflammatory effects of bisdemethoxycurcumin, as well as other curcuminoids, occurred through a mechanism independent of ROS production. This suggests that bisdemethoxycurcumin's ability to reduce inflammation did not rely on the modulation of ROS levels. As an anti-inflammatory effect, modulation of inflammatory signaling and cell proliferation signaling has been found for bisdemethoxycurcumin. In a comparative study, bisdemethoxycurcumin showed lower capacity to hinder TNF-induced NF-κB activation than curcumin and demethoxycurcumin. It should be noted that bisdemethoxycurcumin can hinder of NF-κB or cell proliferation, without effect on reactive oxygen species (ROS) production. Indeed, the anti-inflammatory and anti-proliferative activity of bisdemethoxycurcumin may be related to inducing glutathione (GSH) synthesis [18].

The NF-κB/COX-2 (Cyclooxygenase-2)/iNOS (Inducible nitric oxide synthase) pathway is a well-known mechanism in inflammation, controlling various stages and immune responses. The treatment by Curcumin and its derivatives such as Bisdemethoxycurcumin effectively modulated the NF-κB/COX-2/iNOS pathway, demonstrating a synergistic inhibition of inflammation. anti-inflammatory properties of Curcumin and its derivatives in C. longa because of target TNF-induced NF-κB activation, while MSM suppresses iNOS and COX-2 expression and inhibits IL-6 and TNF-α production through NF-κB [19].

The study which carried out by Li et al, demonstrated bisdemethoxycurcumin significant anti-inflammatory properties, primarily relying on the activation of the nuclear factor erythroid-2 related factor 2 (Nrf2)/heme oxygenase (HO-1) pathway mediated by the PI3K/AKT signaling pathway. Bisdemethoxycurcumin plays a critical role in protecting cardiomyocytes from various forms of damage, with its primary mechanism of action being the activation of the Nrf2/HO-1 pathway. This pathway is known for its potent anti-inflammatory and antioxidant effects, making it a crucial player in cellular protection. The PI3K/AKT pathway serves as the mediator for bisdemethoxycurcumin's activation of Nrf2/HO-1. Through this signaling cascade, bisdemethoxycurcumin effectively reduces inflammation and oxidative stress within cardiomyocytes, contributing to their overall protection and well-being [20].

In another research study, bisdemethoxycurcumin has demonstrated remarkable anti-inflammatory properties by initiating apoptosis through a multitude of signaling pathways within HOS cells. Alongside curcumin and demethoxycurcumin, bisdemethoxycurcumin has exhibited its capacity to induce apoptosis in HOS cells through both caspase-dependent and caspase-independent routes. This dual apoptosis mechanism highlights the adaptability of bisdemethoxycurcumin in addressing inflammation and facilitating cell death, especially in cancerous cells. The involvement of Smad and Akt signaling pathways in these anti-inflammatory effects is noteworthy. Specifically, bisdemethoxycurcumin has been found to trigger caspase-mediated apoptosis in HOS cells by engaging the Smad signaling pathways. Moreover, bisdemethoxycurcumin has demonstrated its ability to induce caspase-mediated apoptosis via the Akt signaling pathway, further accentuating its versatile approach to mitigating inflammation and promoting cell death in HOS cells. This comprehensive understanding of the mechanisms underscores bisdemethoxycurcumin's potential as a therapeutic agent, particularly in the context of conditions related to inflammation and cancer treatment [21].

Neuroprotective effect

Anxiety disorders are one of the most common psychiatric diseases that occur when normally adaptive defensive behaviors, like avoidance of potentially threatening situations, become persistent and intense and severely interfere with life activities. Pathological anxiety behaviors can develop by alterations in GABAergic (Neurons produce gamma-aminobutyric acid (GABA)) inhibitory synaptic transmission [22]. Studies have shown that some heavy metals such as mercury and lead affect the function of the GABAergic, cholinergic, adrenergic, glutamatergic, serotoninergic, and peptidergic neurotransmitter systems and in this way can induce psychiatric disorders like anxiety [23, 24]. Bisdemethoxycurcumin reduces inflammation, protecting against oxidative stress, and modulating the release of serotonin and dopamine [25].

Bisdemethoxycurcumin exhibits remarkable neuroprotective potential, primarily through its antioxidant, anti-inflammatory, and pro-neurogenic properties. It holds promise in shielding nerve cells from oxidative damage, reducing inflammation within neural tissues, stimulating the production of brain-supporting proteins, and safeguarding against neurotoxic substances. Bisdemethoxycurcumin's ability to modulate signaling pathways, protect against excitotoxicity, and inhibit amyloid-beta aggregation further solidifies its neuroprotective role [12, 26].

Alzheimer's disease, a progressive neurodegenerative disorder causes progressive thinking and memory loss and cognitive impairment [27]. This disease results from the extracellular plaque deposits of the amyloid beta (Aβ) protein in the brain in several different molecular forms [28]. Treatment of APP/PS mice with bisdemethoxycurcumin improved cognitive function, decreased oxidative stress, Aβ deposition, and increased the level of sirtuin-1 (SIRT1) expression [29].

Bisdemethoxycurcumin is highlighted for its antioxidative properties, which are crucial in combating the oxidative stress observed in Alzheimer's disease [30]. Oxidative stress results from an imbalance between harmful ROS and the body's ability to neutralize them. This oxidative damage can lead to the degeneration of brain cells and contribute to the progression of Alzheimer's [31, 32]. One key mechanism through which bisdemethoxycurcumin exerts its beneficial effects is by up-regulating SIRT1. SIRT1 is a protein that plays a pivotal role in maintaining cellular health and protecting cells from stress-induced damage. It is known for its involvement in cellular processes such as DNA repair, stress response, and longevity. By enhancing SIRT1 activity, bisdemethoxycurcumin helps promote the overall well-being of brain cells, potentially slowing down the neurodegenerative processes seen in Alzheimer's. So implies that bisdemethoxycurcumin's ability to counteract oxidative stress and support SIRT1 function could make it a promising candidate for Alzheimer's disease treatment or prevention [29].

Parkinson's disease (PD) is a debilitating neurodegenerative condition characterized by the loss of dopamine-producing neurons, with oxidative stress and inflammation playing crucial roles in its development [33, 34]. In a recent study conducted by He and colleagues, the cell-protective properties of bisdemethoxycurcumin were explored in an in vitro model of PD induced by rotenone, a well-known neurotoxin that mimics PD-related cellular damage. The findings from their investigation demonstrated that bisdemethoxycurcumin treatment effectively mitigated the oxidative stress and inflammatory responses triggered by rotenone in neuronal cells. Mechanistically, bisdemethoxycurcumin activated the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) signaling pathway, a crucial player in promoting cell survival and dampening inflammatory processes with upregulation of various genes associated with anti-apoptotic and anti-inflammatory functions. Moreover, the study also observed that bisdemethoxycurcumin treatment led to a reduction in the production of ROS and preserved mitochondrial function in cells exposed to rotenone. These additional findings underscore the neuroprotective potential of bisdemethoxycurcumin, suggesting its ability to combat oxidative stress and maintain proper mitochondrial function, both of which are critical factors in PD pathology [35].

Conclusions

Up-regulation of cleaved caspase-3 and BAX expression and down-regulation of the protein expressions of the XIAP and Bcl-2 in the tumor tissues were found in GBM 8401/luc2 cell xenografts treated by bisdemethoxycurcumin compared to the control

group. Bisdemethoxycurcumin can enhance the permeability of bacterial membranes and inhibit the ATPase. Bisdemethoxycurcumin synergizes conventional antibiotics against MRSA. Because the lack of methoxy groups on the phenyl ring, bisdemethoxycurcumin shows the lower capacity to hinder TNF-induced NF-κB activation compared with curcumin and demethoxycurcumin. The anti-inflammatory and antiproliferative activity of bisdemethoxycurcumin may be related to its increasing effect on GSH levels. In the case of neuroprotective properties, bisdemethoxycurcumin ameliorates cognitive function, reduces oxidative stress and Aβ deposition, and augments the level of SIRT1 expression.

Study Highlights

- Bisdemethoxycurcumin increases the permeability of bacterial membranes and inhibit the ATPase.
- Bisdemethoxycurcumin synergizes conventional antibiotics against MRSA.
- This metabolite shows the lower capacity to hinder TNF-induced NF-κB activation compared with curcumin and demethoxycurcumin.
- The anti-inflammatory and antiproliferative activity of bisdemethoxycurcumin may be related to its increasing effect on GSH levels.
- Bisdemethoxycurcumin ameliorates cognitive function, reduces oxidative stress and Aβ deposition, and augments the level of SIRT1 expression.

Abbreviations

Aβ: Amyloid beta
Bcl-2: B-cell lymphoma 2
COX-2: Cyclooxygenase-2
ERK1/2: Extracellular signal-regulated protein kinases 1 and 2
GABA: Gamma-aminobutyric acid
GBM: Glioblastoma
GRB2: Growth factor receptor-bound protein 2
GSH: Glutathione
IL-1β: Interleukin 1 beta
iNOS: Inducible nitric oxide synthase
IκB-α: IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
JAK2/STAT3: Janus kinase 2/signal transducer and activator of transcription 3
MAPK: Mitogen activated protein kinases
MIC: Minimal inhibitory concentration
MMP-2: Matrix metalloproteinase-2
MRSA: Methicillin-resistant *Staphylococcus aureus*
NF-κB: Nuclear factor-κB
Nrf2/HO-1: Nuclear factor erythroid-2 related factor 2/heme oxygenase
PBP2a: Penicillin-binding protein 2a
PD: Parkinson's disease
PI3K/AKT: Phosphatidylinositol 3-kinase/protein kinase B
RhoA: Ras homolog family member A
ROS: Reactive oxygen species
SIRT1: Sirtuin-1
TNF: Tumor necrosis factor
uPA: Urokinase plasminogen activator
Wnt: Wingless-related integration site
XIAP: X-linked inhibitor of apoptosis protein

Funding

This work was not supported by any institutes.

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, preparing the first draft, and editing.

Acknowledgments

Declared none.

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HOW TO CITE THIS ARTICLE:
Aminnezhad S, Maghsoudloo M, Bagheri Shahzadeh Aliakbari R. Anticancer, antimicrobial, anti-inflammatory, and neuroprotective effects of bisdemethoxycurcumin: Micro and nano facets. Micro Nano Bio Aspects. 2023; 2(4): 17-24.
doi: https://doi.org/10.22034/mnba.2023.416625.1046