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Curcumin and their derivatives with anti-inflammatory, neuroprotective, anticancer, and antimicrobial activities: A review

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ABSTRACT

This review explores the various therapeutic properties of curcumin, derived from turmeric. Curcumin has demonstrated its potential in anti-inflammatory, neuroprotective, anticancer, and antimicrobial applications. It interacts with numerous proteins to combat inflammation and chronic diseases, such as arthritis. In terms of neuroprotection, it helps maintain the blood-brain barrier, reduces oxidative stress, and suppresses inflammation, offering hope for conditions like ischemia. For its anticancer effects, especially in nanoform, curcumin showcases its anti-inflammatory and antioxidant abilities. It inhibits cell proliferation, and invasion, and promotes apoptosis and autophagy. In the antimicrobial realm, curcumin effectively combats bacteria and viruses by disrupting their membranes, quorum sensing systems, and various mechanisms. In conclusion, curcumin's multifaceted properties make it a versatile therapeutic agent with potential in various health applications, including the use of micro or nanoformulations. Extensive research continues to uncover its full capabilities and benefits.

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Introduction

There are numerous biomedical and therapeutic properties for curcuminoids, particularly curcumin. Curcumin ($C_{21}H_{20}O_6$) in two forms of enol and keto can be isolated from *Curcuma longa* (turmeric) related to Zingiberaceae family (Figure 1) [1]. Anticancer, anti-inflammatory, neuroprotective, antibacterial, antifungal, and antiviral activities have been reported for curcumin [2]. Despite the abundant therapeutic effects of curcumin, poor bioavailability is the major limitation for obtaining effective formulas in physiological conditions [3]. Loading and encapsulation of curcumin similar to other polyphenols [4, 5] can be possible by various organic, semi-organic, and inorganic nanomaterials [6]. In this review, we have presented novel aspects of micro and nanoformulations for the improvement of the anti-inflammatory, anticancer, antimicrobial, and neuroprotective effects of curcumin.

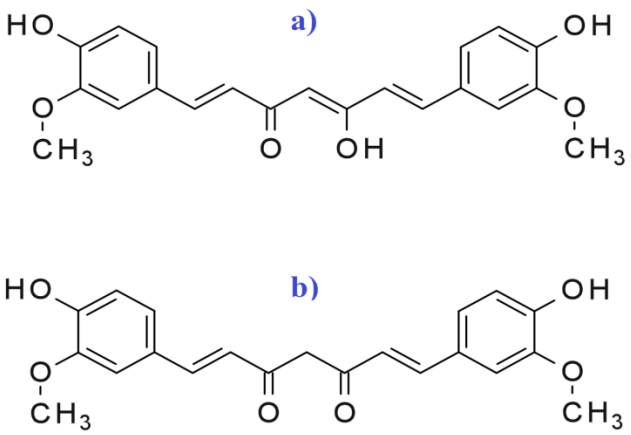

Fig. 1. Curcumin in two forms of enol (a) and keto (b) can be isolated from turmeric.

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Anti-inflammatory effect

Curcumin compared to its analogues such as demethoxycurcumin and bisdemethoxycurcumin exhibits more anti-inflammatory effects because of the major function of methoxy groups on the phenyl ring [7]. In recent years, there has been a notable shift in medical practice towards prioritizing prevention and phytotherapy over the reliance on anti-inflammatory drugs with well-documented side effects [8]. Chronic inflammation is now recognized as a pivotal factor in the development of numerous chronic diseases, prompting extensive research into natural extracts possessing immunosuppressive and anti-inflammatory properties [9]. Among these natural compounds, curcumin, resveratrol, and quercetin have emerged as prominent candidates due to their capacity to modulate cell signaling pathways associated with inflammatory conditions [10]. Curcumin, in particular, has garnered considerable attention owing to its interaction with over 30 different proteins, making it a versatile player in the battle against inflammation [11, 12]. Notably, curcumin has been shown to inhibit nuclear factor-κB (NF-κB), a central transcription factor in inflammatory diseases, thereby exerting its potent anti-inflammatory and immunosuppressive effects [13].

Numerous studies have demonstrated the therapeutic potential of curcumin in mitigating the progression of arthritis and other inflammatory conditions [14]. Arthritis, characterized by a strong inflammatory component, involves key cytokines like tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1 [15]. Curcumin has been found to inhibit the production and activity of crucial markers associated with inflammation, including TNF-α, NF-κB, cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR), and interleukins. This multifaceted action enables curcumin to effectively reduce inflammation in diseases such as arthritis, psoriasis, inflammatory bowel disease, and asthma [16]. One intriguing mechanism through which curcumin exerts its anti-inflammatory effects is by interacting with peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ is a nuclear receptor that plays a pivotal role in regulating various cellular processes, including inflammation and immune responses [17]. Upon activation, PPAR-γ has the capability to suppress the expression of pro-inflammatory genes while promoting anti-inflammatory pathways [18].

This interaction between curcumin and PPAR-γ holds significant promise in the realm of potential therapeutics, particularly for conditions marked by chronic inflammation, including certain autoimmune disorders, metabolic diseases, and neurodegenerative conditions. However, it's important to acknowledge that ongoing research is essential to fully unravel the extent of curcumin's therapeutic potential and the precise mechanisms underlying its interaction with PPAR-γ [19, 20].

Neuroprotective effect

Complexes of manganese with curcumin and their derivatives including diacetylcurcumin and ethylenediamine have been utilized for assessment of their superoxide dismutase and anti-lipid peroxidation activity. These metal complexes showed a remarkable ability to reduce peroxidation by IC_{50} of 26.3 μM, higher superoxide dismutase (SOD) activity, and the significant inhibitory activity to hydrogen peroxide (H_2O_2)-induced cell damage at a concentration of 0.1 ppm compared with pure curcumin and their derivatives. Indeed, these complexes can mimic SOD and penetrates the brain for control of brain neurotransmitters [21]. Curcumin exhibits robust antiapoptotic effects in the context of cerebral ischemia, a condition characterized by neuronal cell death primarily through apoptosis, the prevailing mode of neurodegeneration in this scenario. Numerous studies underscore curcumin's neuroprotective attributes. It mitigates apoptotic neuronal demise by diminishing proapoptotic factors like Bax and caspase-3, concurrently elevating antiapoptotic factors such as Bcl-2. These protective effects are consistently observed across diverse experimental models of cerebral ischemia, encompassing rodents and neuronal cell cultures. Importantly, curcumin's antiapoptotic influence extends beyond neurons to encompass other central nervous system cells like astrocytes [22]. Furthermore, curcumin's antioxidant properties extend to enhancing the activity of crucial antioxidant enzymes such as SOD and glutathione peroxidase (GSH-px). This comprehensive effect of curcumin effectively reduces oxidative reactions and bolsters the performance of antioxidant enzymes in the postischemic brain [23]. Additionally, curcumin,

known for its potent anti-inflammatory properties, showcases remarkable potential in mitigating inflammatory responses within the ischemic brain [24]. A pivotal target of curcumin's action is the NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome, a key contributor to the inflammatory cascade in cerebral ischemia [25]. Curcumin adeptly inhibits NLRP3 inflammasome activation, resulting in a significant reduction in the release of proinflammatory cytokines like IL-1β and IL-6 [26]. Furthermore, curcumin intervenes in intracellular signaling pathways, including mitogen-activated protein kinase (MAPK) and NF-κB, which are pivotal regulators of inflammation [27]. Consequently, there is a substantial decrease in the production of proinflammatory mediators.

The inhibition of NLRP3 inflammasome is a new therapeutic approach to ischemic stroke for protecting injured neurons. By controlling effector molecules in the brain, curcumin, a strong inhibitor of NLRP3 inflammasome, has been proven to protect neurons from damage caused by ischemic stroke and neurological conditions. In this review, we evaluated how NLRP3 is activated by several pathways after ischemic stroke. Curcumin as a neuroprotective drug inhibits ROS formation and regulates microglia M1/M2 and gut microbiota to mitigate inflammation. The upstream and downstream pathways were clarified to show how curcumin regulates NLRP3 inflammasome to affect neuroinflammation and BBB integrity following ischemic stroke. The toll-like receptor 4 (TLR4)/NF-κB autophagy-related mediators and cell energy metabolism pathways were also clarified and the precise mechanisms shown by which curcumin affects the NLRP3 inflammasome (Figure 2) [28].

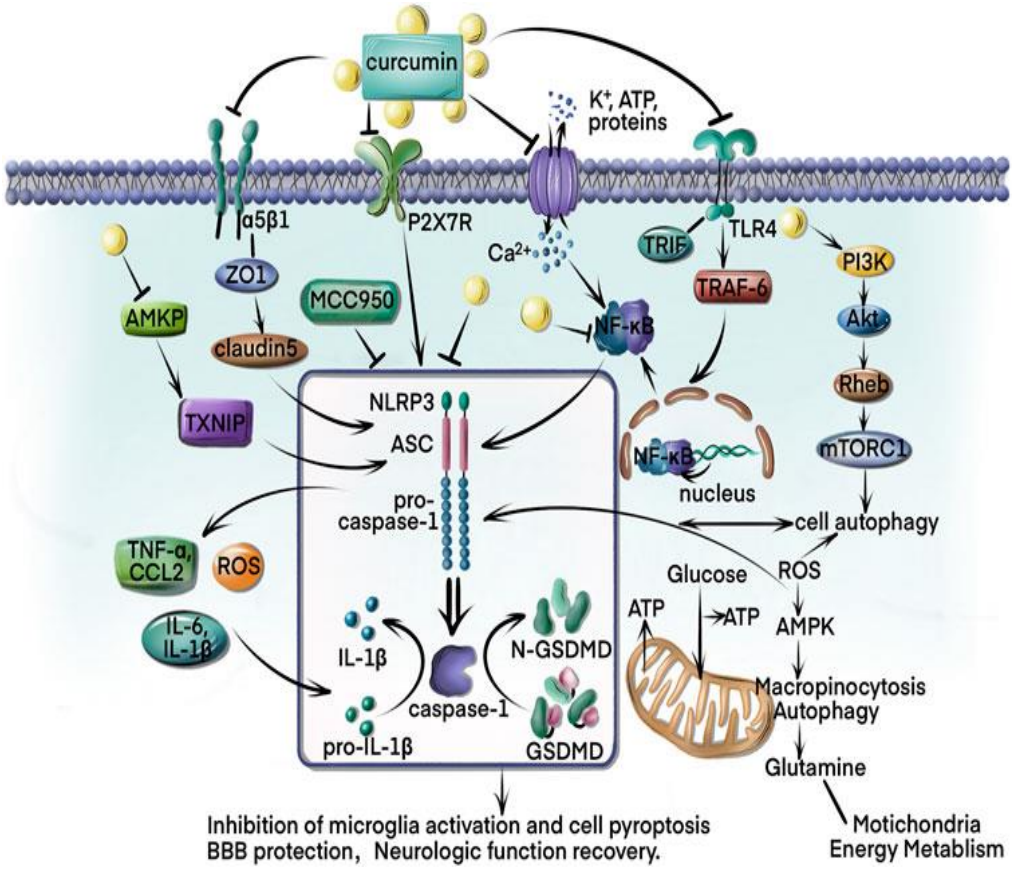

Fig. 2. Mehcnisms illustrating how curcumin modulates the NLRP3 inflammasome (Extracted from [28]).

Curcumin exhibits neuroprotective properties by effectively preserving the integrity of the blood-brain barrier (BBB) during instances of ischemic injury.

Disruption of the BBB is a pivotal event that can lead to brain damage following ischemia. This disruption involves the structural degradation of tight junction proteins that exist between brain endothelial cells,

thereby permitting harmful substances and immune cells to infiltrate the brain [29]. Curcumin's neuroprotective impact primarily hinges on its capacity to counteract this BBB disruption. Experimental studies have demonstrated that curcumin treatment enhances the resilience of brain microvascular endothelial cells (BMECs) and elevates the expression of tight junction proteins like ZO-1 and occludin [30]. In various animal models, the administration of curcumin has resulted in a significant reduction in leakage through the brain's vasculature, indicating its crucial role in preserving BBB integrity. Additionally, curcumin has proven effective in diminishing the expression of adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), which are vital for immune cell infiltration into the brain [31].

Curcumin's remarkable anti-inflammatory abilities are not confined to a single ischemic model; they extend across diverse scenarios such as subarachnoid hemorrhage, intracerebral hemorrhage, and middle cerebral artery occlusion. This versatility is characterized by its ability to curb the release of inflammatory molecules, including COX-2, IL-1β, IL-6, TNF-α, inducible nitric oxide synthase (iNOS), VCAM, ICAM-1, and NF-κB, collectively contributing to its potent anti-inflammatory properties [27]. Moreover, curcumin goes beyond merely suppressing inflammation; it actively promotes the integrity of the neurovascular system. It achieves this by reducing the infiltration of peripheral immune cells and orchestrating a shift in the polarization of microglia/macrophages from the proinflammatory M1 state to the anti-inflammatory M2 state. In summary, curcumin's anti-inflammatory effects in the context of cerebral ischemia encompass the inhibition of MAPKs and NF-κB activation, the suppression of proinflammatory mediator production, and the modulation of glial cell polarization [32].

Autophagy assumes a dual role in the aftermath of cerebral ischemia, exhibiting both neuroprotective and neurodegenerative effects [33]. Curcumin, recognized for its neuroprotective properties, is associated with the inhibition of autophagic processes in the context of cerebral ischemia. Experimental studies have revealed that the administration of curcumin leads to a substantial decrease in the expression of microtubule-associated protein light chain 3 (LC3), an established marker of autophagy, while simultaneously elevating the levels of p62 in the brains of rats afflicted by ischemic injury. These effects are also mirrored in PC12 cells subjected to oxygen-glucose deprivation and reoxygenation (OGD/R), where curcumin treatment results in reduced LC3 II/I levels, along with decreased phosphorylation of mTOR and Akt (protein kinase B) in the post-ischemic brain. In PC12 cells exposed to OGD/R, curcumin effectively downregulates LC3 II/I and hypoxia-inducible factor 1-alpha (HIF-1α) expression while enhancing p62 expression. In summary, curcumin's multifaceted neuroprotective effect actions make it a promising candidate for neuronal damage in cerebral ischemia [32].

Moreover, curcumin boasts potent antioxidant properties that assume a pivotal role in shielding the brain from oxidative stress following ischemic injury. In both in vitro and in vivo models of ischemia, curcumin adeptly curtails the generation of free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Furthermore, it acts to inhibit enzymes that contribute to heightened oxidative stress [34].

Anticancer effect

Curcumin, specifically nanocurcumin is well-known for its anti-inflammatory and antioxidant properties, making it a promising candidate for enhancing cancer treatment outcomes [35]. However, despite these advancements, tumors have developed strategies to evade the immune system within the tumor microenvironment (TME) [36]. These strategies include inhibiting anti-tumor T cells and creating immune-resistant phenotypes. A critical aspect of the tumor cells' immune evasion strategy involves transforming the immunogenic TME into a tolerogenic one [37]. Concurrently, surviving tumor cells adopt an immune-resistant phenotype, characterized by a reduction in IFN-γ release and the induction of T-cell exhaustion. This is achieved through the production of various immune escape mediators and signaling pathway modulators, such as stromal barriers in the TME, Treg cells, and immune checkpoint inhibitors In total, there are eight common immune evasion strategies by tumor cells, which have been illustrated in Figure 3 [38]. Curcumin, functioning as an immunomodulator, interacts not only with various

cellular components like dendritic cells, macrophages, natural killer cells, and both B and T lymphocytes but also with regulatory molecules involved in inflammation and cell proliferation processes and their downstream signaling pathways. In recent times, curcumin has garnered significant therapeutic interest in treating neoplastic diseases due to its anti-inflammatory and anti-proliferative properties. Curcumin's anti-cancer properties also involve the modulation of several signaling pathways related to mutagenesis, oncogene expression, cell cycle regulation, apoptosis, angiogenesis, and metastasis [39] . Curcumin, employs a multifaceted approach to combat this complex disease which illustereted in figure4. Curcumin's multifaceted mechanisms in cancer management are characterized by its ability to inhibit cell proliferation through Wingless-related integration site (Wnt)/β-catenin pathway disruption and modulation of key regulatory proteins. It efficiently suppresses cell migration and invasion by targeting the transforming growth factor-beta (TGF-β) / SMAD (mothers against decapentaplegic) 2/3 pathway, favoring anti-metastatic factors. Moreover, curcumin generates ROS via p38 MAPK, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) pathways, simultaneously triggering ferroptosis, a unique cell death process. The promotion of apoptosis involves upregulating pro-apoptotic proteins while downregulating anti-apoptotic factors. Curcumin further stimulates autophagy, modulates gut microbiota, and reduces cancer stemness by regulating octamer-binding transcription factor 4 (OCT4), sex-determining region Y-box 2 (SOX2), and Nanog through the Janus kinase/signal transducers and activators of transcription 3 (JAK/STAT3) pathway inhibition. Additionally, curcumin alleviates inflammation by blocking the TLR4/NF-κB pathway and inhibits angiogenesis by suppressing angiogenic factors. Its comprehensive actions highlight its potential as an effective strategy for cancer prevention and treatment.[40].

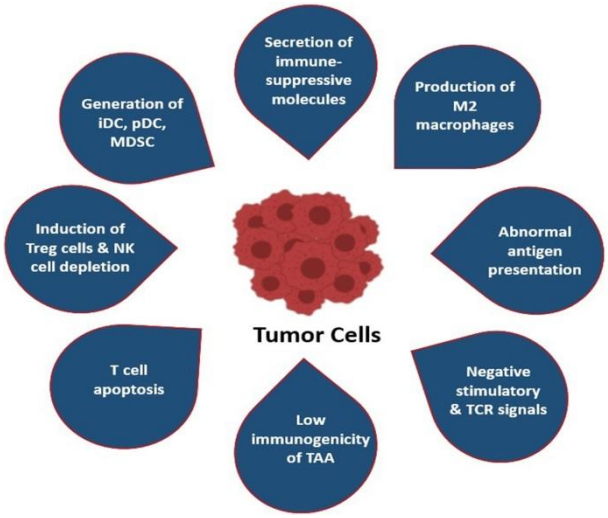

Fig. 3. Schematic image showing eight common immune evasion strategies by tumor cells (Adopted from [38]).

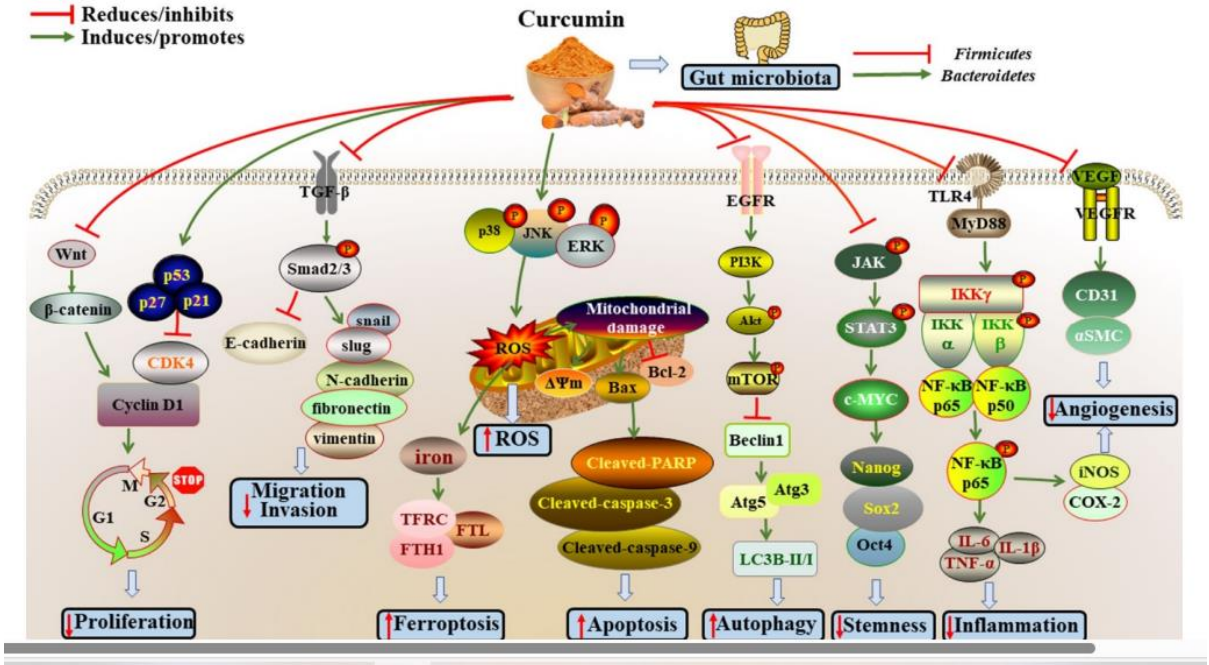

Fig. 4. The main effects and mechanisms of curcumin on cancers (Extracted from [40]).

Antimicrobial effect

Curcumin has remarkable antimicrobial properties against a wide spectrum of microorganisms, including bacteria, viruses, fungi, and parasites [41]. Unlocking the antiviral potential of curcumin within the host cell involves a nuanced understanding of its chemotherapeutic actions, strategically targeting key stages in the viral life cycle. These pivotal steps encompass the initial attachment of the virion to its cellular receptor, the subsequent penetration of the host cell, viral genome transcription and replication, translation, virion assembly, and eventual release. Curcumin steps into this complex dance, orchestrating a defense against viral invaders. Curcumin's multifaceted approach begins by thwarting the activity of viral envelope proteins, effectively halting viral attachment and entry. It then proceeds to modulate specific signaling pathways, mitigating inflammation and fine-tuning the cellular translation and transcription machinery. This intricate orchestration serves as a barricade against viral replication. Beyond these measures, curcumin deploys a potent virucidal effect by disrupting the integrity of the viral envelope itself. Curcumin's diverse range of antiviral mechanisms positions it as a versatile fighter against a variety of viruses, each falling under its protective umbrella [42].

In the realm of antibacterial action, curcumin emerges as a potent force, employing versatile mechanisms to combat a wide array of bacterial adversaries, including those that have developed antibiotic resistance. Curcumin's effectiveness extends to combatting microorganisms responsible for surgical infections and implant-related bone infections, with a primary focus on pathogens like Staphylococcus aureus and Escherichia coli. Notably, its potential to combat Helicobacter pylori and Mycobacterium tuberculosis, either alone or in combination with traditional antibiotics, represents one of its most promising antibacterial attributes[41].

In the first facet of its antibacterial capabilities, curcumin, along with its counterparts including demethoxycurcumin and bisdemethoxycurcumin orchestrates a formidable attack on bacterial cell membranes, disassembling their structural integrity and permeability. This disruptive action spans both Gram-positive and Gram-negative bacterial domains, ultimately culminating in the demise of bacterial cells. Curcumin's distinctive lipophilic structure facilitates its direct integration into liposome bilayers, thereby significantly enhancing their permeability [43].

Moreover, curcumin delves into the intricate domain of bacterial quorum sensing (QS) systems, the master regulators governing the formation of biofilms-an integral component in approximately 80% of microbial infections. Armed with the capacity to inhibit bacterial QS systems, curcumin disrupts the fundamental processes underlying biofilm development. These compounds have the ability to disrupt the quorum sensing pathways S-ribosylhomocysteine lyase (LuxS)/autoinducer-2 (AI-2) in *Bacillus subtilis* and LasI/LasR in Pseudomonas aeruginosa. By interfering with these signaling systems, these natural compounds may have the potential to inhibit bacterial growth and the expression of virulence factors, which could be useful in developing new strategies for combating bacterial infections [44].

Other diverse range of mechanisms was deployed by curcumin to combat bacterial infections comprehensively. From inhibiting bacterial cell division through interactions with the essential filamentous temperature-sensitive protein Z (FtsZ), that In the case of molecular docking, methoxy functional groups linked to phenolic rings, two carbonyl groups, and the oxygen molecules of phenol can interact with the catalytic site of FtsZ, the cytoskeletal protein using forming hydrophobic interactions and hydrogen bonds [33, 36].

Finally extensive research has unveiled the multifaceted molecular mechanisms behind curcumin's antibacterial properties. These mechanisms encompass disrupting bacterial membranes, inhibiting the production of virulence factors and biofilm formation, inducing oxidative stress leading to programmed cell death, causing bacterial metabolic disturbances, and displaying phototoxicity. These characteristics underscore curcumin's role as a versatile, broad-spectrum antibacterial agent. Notably, it exhibits additive or synergistic effects when combined with conventional antibiotics or various non-antibiotic compounds, including other antibacterial agents, natural products, and metals. Furthermore, both animal experiments and human clinical trials have highlighted

curcumin's excellent safety profile, further enhancing its appeal as a potential antibacterial agent and adjuvant in the fight against bacterial infections [41, 45].

Conclusions

There are numerous therapeutic applications for curcumin and other curcuminoids in both micro- and nano-formulations. Antioxidant, anti-inflammatory, anticancer, antibacterial, antiviral, antifungal, and neuroprotective activities have been reported for this polyphenolic compound. Indeed, the unveiling of the therapeutic mechanisms of curcumin is not yet completely understood and more *in silico*, *in vitro*, and *in vivo* studies are required to address this issue. In this regard, nanoformulations based on organic, inorganic, and semi-organic nanomaterials can be promising nanocarriers for loading, encapsulation, and delivery of curcumin to specific tissue. Curcumin, specifically nanocurcumin is well-known for its anti-inflammatory and antioxidant properties, making it a promising candidate for increasing anticancer activity. This metabolite, identified for its neuroprotective properties, is associated with the inhibition of autophagic processes in the context of cerebral ischemia. Complexes of manganese with curcumin and their derivatives including diacetylcurcumin and ethylenediamine can mimic SOD and penetrates the brain for control of brain neurotransmitters. Experimental and *in silico* studies have illustrated the major role of the hydroxyl and methoxy groups of curcumin in antimicrobial activity. These compounds present a spectrum of health benefits, spanning antioxidant, anti-inflammatory, anticancer, antibacterial, antiviral, antifungal, and neuroprotective properties. While we continue to unravel the underlying mechanisms of these effects, ongoing research is imperative. Particularly noteworthy is curcumin's potential in cancer management, manifested through its multifaceted actions, from restraining cell proliferation to inducing apoptosis, promoting autophagy, modulating gut microbiota, and reducing cancer stemness.

In the realm of antimicrobial effects, curcumin demonstrates encouraging prospects, disrupting bacterial cell membranes, inhibiting quorum sensing systems, and employing diverse mechanisms to combat bacterial infections. Collectively, curcumin and its derivatives hold significant promise across a spectrum of therapeutic applications, especially when harnessed within nanoformulations. In conclusion, this comprehensive review underscores the therapeutic promise of curcumin and its derivatives within micro- and nano-formulations. Further exploration and investigation are crucial to fully realize their potential and harness their manifold benefits for human health.

Study Highlights

- Curcumin, identified for its neuroprotective properties, is associated with the inhibition of autophagic processes in the context of cerebral ischemia.
- Complexes of manganese with curcumin and their derivatives including diacetylcurcumin and ethylenediamine mimic SOD and penetrates the brain for control of brain neurotransmitters.
- Curcumin can cause disrupting bacterial cell membranes and inhibiting quorum sensing systems.
- There are the therapeutic promise of curcumin and its derivatives within micro- and nano-formulations.

Abbreviations

AI-2: Autoinducer-2
Akt: Protein kinase B
BBB: Blood-brain barrier
BMECs: Brain microvascular endothelial cells
COX-2: Cyclooxygenase-2
ERK: Extracellular signal-regulated kinase
FtsZ: Filamentous temperature-sensitive protein Z
GSH-px: Glutathione peroxidase
HIF-1α: Hypoxia-inducible factor 1-alpha
ICAM-1: Intercellular adhesion molecule 1
IL: Interleukin
iNOS: Inducible nitric oxide synthase
JAK/STAT3: Janus kinase/signal transducers and activators of transcription 3
JNK: c-Jun N-terminal kinase
LC3: Microtubule‑associated protein light chain 3
LuxS: S-ribosylhomocysteine lyase
MAPK: Mitogen-activated protein kinase
mTOR: Mammalian target of rapamycin
NF-κB: Nuclear factor-κB
NLRP3: Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3
OCT4: Octamer-binding transcription factor 4

OGD/R: Oxygen-glucose deprivation and reoxygenation
PPAR-γ: Peroxisome proliferator-activated receptor-γ
QS: Quorum sensing
RNS: Reactive nitrogen species
ROS: Reactive oxygen species
SMAD: mothers against decapentaplegic
SOD: Superoxide dismutase
SOX2: Sex-determining region Y-box 2
TGF-β: Transforming growth factor-beta
TLR4: Toll-like receptor 4
TME: Tumor microenvironment
TNF-α: Tumor necrosis factor-α
VCAM-1: Vascular cell adhesion molecule 1
Wnt: Wingless-related integration site

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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, preparing the first draft, and editing.

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