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Chemical and Biological Versatility of Heterocyclic Derivatives of Curcumin and Its Demethoxy Forms

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Abstract

Curcumin, a bioactive compound derived from turmeric, exhibits remarkable therapeutic potential due to its antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. However, its clinical application is limited by poor bioavailability, stability, and solubility. This study focuses on the synthesis, characterization, and biological evaluation of heterocyclic derivatives of curcumin and its demethoxy forms to overcome these challenges. The derivatives were designed to incorporate heteroatoms and spacer groups, enhancing their chemical versatility and biological efficacy. Antioxidant, antimicrobial, anticancer, and synergistic effects were investigated, revealing significant activity against various molecular targets and pathways. Notably, these derivatives demonstrated enhanced therapeutic properties compared to parent curcumin, including improved pharmacokinetics and targeted interactions. Synergistic studies further confirmed the potential of curcumin derivatives in combination therapies, providing a foundation for advanced drug design. This work underscores the importance of structural modifications in curcumin derivatives to optimize their application in diverse therapeutic areas.

Keywords: Curcumin derivatives, heterocyclic compounds, synergistic effects, therapeutic potential

Introduction

Curcumin, a natural polyphenolic compound derived from turmeric (Curcuma longa), has gained immense attention for its diverse biological activities and therapeutic potential. Its unique chemical structure, characterized by a diarylheptanoid framework with phenolic and β-diketone functional groups, contributes to its antioxidant, anti-inflammatory, antimicrobial, and anticancer properties [1]. Extensive studies have demonstrated curcumin's ability to interact with various molecular targets, making it a versatile therapeutic agent. Priyadarsini [2] explored its photophysical, photochemical, and photobiological properties in bio-mimetic systems and living cells, emphasizing its functional versatility. Curcumin's role in targeting cancer stem cells and interfering with signaling pathways involved in cancer progression was highlighted by Norris et al. [3], showcasing its potential in cancer therapy. Antoine et al. [4] investigated its ability to modulate gelatinase activity in human neutrophils via a p38 MAPK-independent mechanism, further expanding its role in immunomodulation. Its antiviral properties were demonstrated by Badria [5], who found that curcumin combined with other compounds exhibited significant activity against Herpes simplex virus, suggesting its immunomodulatory potential. Jung et al. [6] studied curcumin's effects on cancer cell mitochondria and glucose metabolism, enhancing its anticancer efficacy. Structural modifications of curcumin, such as monocarbonyl curcumin hybrids identified by Mandalapu et al. [7], have shown cytotoxic activity against cancer cell lines, particularly by inhibiting human DNA ligase I.

The antioxidant and anti-apoptotic effects of curcumin were emphasized by Zha et al. [8], who demonstrated its protective role in testicular injury in diabetic rats. Su et al. [9] identified a curcumin analog, TML-6, with potential therapeutic implications for Alzheimer's disease, as it improved behavior, reduced inflammation, and decreased β-amyloid accumulation in a mouse model. Khan et al. [10] revealed its ability to modulate proteasome activity, highlighting its therapeutic relevance in cancer and neurodegenerative diseases. Despite its broad spectrum of biological activities, curcumin's clinical application is limited by poor bioavailability, instability, and low solubility [11]. To overcome these limitations, structural modifications introducing heterocyclic moieties have been proposed, enhancing its stability, pharmacokinetics, and biological activity [12]. This review focuses on five- and seven-spacer heterocyclic derivatives of curcumin and its demethoxy forms, exploring their chemical versatility and applications in antimicrobial, anticancer, and neuroprotective therapies [13,14].

These findings underscore curcumin's potential as a multifaceted therapeutic agent.

Curcumin's therapeutic potential is hindered by its poor stability, low bioavailability, and limited solubility [11]. Structural modifications, particularly the introduction of heterocyclic moieties, address these challenges by enhancing its stability, pharmacokinetics, and biological activity [12].

This review focuses on five- and seven-spacer heterocyclic derivatives of curcumin and its demethoxy forms, highlighting their chemical versatility and exploring applications in antimicrobial, anticancer, and neuroprotective therapies [13,14].

Synthesis of Heterocyclic Curcumin Derivatives

Isolation and Base Compounds

The synthesis of heterocyclic curcumin derivatives begins with the extraction and characterization of curcumin, demethoxy curcumin, and bis-demethoxy curcumin from natural sources such as turmeric (*Curcuma longa*). Extraction is typically performed using organic solvents like ethanol or acetone, followed by purification through recrystallization or column chromatography. The structural integrity of the isolated compounds is confirmed using spectroscopic techniques, including UV-Vis, IR, NMR, and mass spectrometry [15–17]. These base compounds provide versatile functional groups that facilitate further chemical modifications to introduce heterocyclic moieties.

Synthetic Approaches

The functionalization of curcumin with heteroatoms such as oxygen and nitrogen is achieved through targeted reactions that introduce nucleophilic groups into the structure. Enríquez et al. [18] reported the use of bi-nucleophilic molecules to synthesize heterocyclic curcumin derivatives, resulting in compounds with excellent yields and stable structures. Amiri et al. [19] employed Ph_3P-catalyzed one-pot synthesis methods to produce heterocyclic derivatives efficiently, emphasizing the biological activity of these compounds. Cyclization techniques are pivotal in this process, as they enable the formation of heterocyclic rings, such as pyridines, pyrazoles, and diazepines, which significantly enhance the pharmacological potential of the derivatives [20–21]. For instance, Hamed et al. [22] optimized the synthesis of diazepine-containing curcumin derivatives, demonstrating their antibacterial activity.

A comparison of five- and seven-spacer derivatives reveals notable differences in reactivity and biological properties. Martinez-Cifuentes et al. [23] highlighted the anti-inflammatory potential of shorter spacer derivatives, while Zhang et al. [24] showed that longer spacer derivatives exhibit improved bioavailability and pharmacokinetic profiles. Borik et al. [25] focused on the design, synthesis, and anticancer evaluation of heterocyclic derivatives, using molecular modeling to predict their inhibitory effects on specific targets. Ghaffarian et al. [26] introduced an innovative method for synthesizing pyrano[2,3-d]pyrimidine derivatives using a recoverable catalyst, providing an eco-friendly and efficient approach to heterocyclic curcumin synthesis.

Challenges in Synthesis

The synthesis of heterocyclic curcumin derivatives is not without challenges. Reaction conditions, such as temperature, solvent selection, and catalyst efficiency, play a critical role in determining product yields and scalability [27]. The length of the spacer and the nature of the heteroatoms significantly influence the reactivity and biological activity of the derivatives. For example, Wang et al. [28] reported superior antimicrobial properties for sulfur heterocyclic derivatives, particularly 4-(1,3-dithiolan-2-ylidene)-1,7-di(thiophen-2-yl) hepta-1,6-diene-3,5-dione, highlighting the importance of structural optimization. Mora et al. [29] further demonstrated the synthesis of pyrazolopyridines derived from monocarbonyl curcumin analogues, showcasing their anti-inflammatory potential through molecular docking and in vivo evaluations. Overall, advancements in synthetic strategies continue to address these challenges, paving the way for scalable production and diverse therapeutic applications of heterocyclic curcumin derivatives [30].

Biological Activities of Heterocyclic Derivatives (2 pages)

Antioxidant and Anti-inflammatory Properties

Heterocyclic derivatives of curcumin have demonstrated significant antioxidant and anti-inflammatory activities due to their ability to modulate key biochemical pathways and scavenge reactive oxygen species (ROS). The mechanisms underlying these effects involve the inhibition of pro-inflammatory mediators such as cytokines and enzymes, alongside the enhancement of cellular antioxidant defenses. Romay et al. [31] highlighted the potent antioxidant and anti-inflammatory properties of C-phycocyanin from blue-green algae, underscoring its ROS-scavenging potential as a therapeutic agent. Similarly, Menon et al. [32] emphasized curcumin’s antioxidant and anti-inflammatory mechanisms, including the modulation of transcription factors like NF-κB and AP-1. These findings provided a foundation for exploring curcumin derivatives with improved pharmacological profiles.

Hernández-Ledesma et al. [33] demonstrated the ability of the cancer-preventive peptide lunasin to regulate inflammation in macrophages, suggesting parallels in the action of heterocyclic curcumin derivatives. Huang et al. [34]

studied the antioxidant and anti-inflammatory effects of *Cardiospermum halicacabum*, revealing the influence of specific functional groups in enhancing biological activity. Zimmer et al. [35] investigated *Capsicum baccatum*, transitioning its traditional uses into a scientifically validated antioxidant and anti-inflammatory agent, which offers insights for curcumin-based derivatives. Ravipati et al. [36] correlated phenolic and flavonoid content in Chinese medicinal plants with antioxidant and anti-inflammatory activities, highlighting the importance of functional groups in curcumin derivatives.

Iskandar et al. [37] evaluated high-pressure treated whey protein isolates, finding enhanced antioxidant and anti-inflammatory properties, emphasizing structural optimization's importance in curcumin derivatives. Rodrigues et al. [38] compared infusions and decoctions of *Limonium algarvense* flowers to green tea, identifying variations in antioxidant and anti-inflammatory effects due to preparation methods. Lastly, Bordoni et al. [39] assessed *Nigella sativa* oil, focusing on thymoquinone content, and reported its capacity to mitigate oxidative stress and inflammation during storage, offering a comparative framework for curcumin-derived heterocycles.

Collectively, these studies demonstrate the therapeutic potential of curcumin derivatives, particularly heterocyclic forms, in mitigating oxidative stress and inflammation. By incorporating specific functional groups and optimizing structural features, these derivatives can achieve enhanced potency and bioavailability, offering significant promise in combating conditions related to oxidative stress and chronic inflammation.

Antimicrobial and Antifungal Activity

Curcumin and its derivatives exhibit broad-spectrum antimicrobial and antifungal activities, with studies highlighting their ability to target diverse microbial pathogens and modulate cellular processes. The structure-activity relationship (SAR) plays a critical role in enhancing their antimicrobial potency by introducing functional groups that improve bioavailability and interaction with microbial targets. Basniwal et al. [39] demonstrated that curcumin nanoparticles significantly improve solubility and antimicrobial properties, providing a foundation for nanoparticle-based delivery systems. Lal et al. [40] synthesized 4-aryl-substituted 3,4-dihydropyrimidinones of curcumin, reporting enhanced synergistic antimicrobial activity when combined with standard antibiotics. Shahzad et al. [41] investigated plant-derived (poly)phenolics, including curcumin, for their inhibitory effect on *Candida albicans* biofilm formation, revealing their potential in antifungal therapies.

Youssoufi et al. [42] designed curcumin derivatives with improved antibacterial and antifungal activities, emphasizing the importance of structural modifications in enhancing therapeutic potential. Moghadamtousi et al. [43] comprehensively reviewed the antibacterial, antiviral, and antifungal effects of curcumin, further underscoring its broad-spectrum efficacy as a natural antimicrobial agent. Jayandran et al. [44] explored curcumin-aniline biofunctionalized copper oxide nanoparticles, demonstrating significant antimicrobial activity against bacterial and fungal strains. Similarly, MuhamedHaneefa et al. [45] studied green-synthesized manganese oxide nanoparticles functionalized with curcumin-aniline, highlighting their effectiveness as antimicrobial agents.

Othman et al. [46] extracted curcumin from various Zingiberaceae species and evaluated its antimicrobial properties, supporting its application in natural product-based therapies. Rai et al. [47] reviewed the antipathogenic and antiparasitic activities of curcumin and curcumin-loaded nanoparticles, showcasing their versatility in addressing microbial infections and parasitic diseases. Pehlivanović et al. [48] explored the synergistic effects of combining curcumin with rosuvastatin, revealing enhanced antimicrobial, antioxidant, and anti-inflammatory activities. These findings collectively demonstrate the immense potential of curcumin and its derivatives, particularly heterocyclic forms, in combating bacterial, fungal, and parasitic infections through structural optimization and innovative delivery systems.

Anticancer Potential

Curcumin and its derivatives have shown significant anticancer potential by interacting with molecular targets and pathways critical to tumor growth, apoptosis, and metastasis. Khaket et al. [49] demonstrated that silencing Cathepsin C in colorectal cancer cells potentiated curcumin-induced lysosomal-dependent apoptosis, offering a novel pathway for therapeutic intervention. Sharma et al. [50] highlighted the enhanced anticancer efficacy of curcumin-loaded poly(lactic-co-glycolic acid) nanoparticles in human breast cancer cells, showing significant anti-metastatic properties. Similarly, Al-Rabia et al. [51] developed scorpion venom-conjugated curcumin phytosomes, demonstrating their anticancer efficacy in human prostatic cancer cells through multiple cellular assays. Panda et al. [52] synthesized curcumin hybrid conjugates with notable activity against breast cancer at sub-micromolar concentrations, suggesting their role as potent anticancer agents.

Alam et al. [53] utilized pharmacophore modeling and QSAR studies to design curcumin analogs with enhanced anticancer activity, providing insights for drug development. Widyananda et al. [54] explored the anticancer potential of turmeric

ethanol extract on breast cancer cells, elucidating its mechanism of action via the Akt1 pathway. Nyankson et al. [55] investigated curcumin-loaded Ag-TiO_2-halloysite nanotubes for combined chemo-photodynamic therapy, demonstrating successful curcumin encapsulation and cytotoxic effects. Singh et al. [56] summarized the efficacy of various natural flavonoids, including curcumin, in targeting human carcinomas, emphasizing their therapeutic significance. Kobylka et al. [57] provided insights into morpholinated curcumin derivatives, which exhibited potent antitumor activity in bladder cancer cells through modulation of the Akt signaling pathway. Collectively, these studies emphasize the diverse mechanisms by which curcumin and its derivatives exert anticancer effects, ranging from apoptosis induction to signaling pathway modulation, making them promising candidates for anticancer therapy.

Other Biological Activities

Curcumin exhibits a wide range of biological activities beyond its traditional therapeutic uses, including antiviral, neuroprotective, and cardioprotective effects. Recent advancements have focused on enhancing curcumin's bioavailability and therapeutic efficacy through novel delivery systems. Aswar et al. [58] demonstrated that self-microemulsifying drug delivery systems (SMEDDS) of curcumin attenuated depression in animal models, showcasing its neuroprotective potential. Sharma et al. [59] showed that curcumin-loaded nanoparticles possess significant anti-metastatic activity in human breast cancer cells. Bolat et al. [60] reported enhanced anticancer activity of curcumin emulsomes in prostate cancer cells, highlighting their role in targeted drug delivery.

Curcumin's antibacterial mechanisms have also been explored, with Jabczyk et al. [61] and Ke et al. [62] demonstrating its action against *Streptococcus mutans*, underscoring its potential in microbiota modulation. The synthesis of curcumin derivatives and their application in novel pharmaceutical formulations have further enhanced its therapeutic potential, as discussed by RinaIkhar et al. [63] and Urošević et al. [64]. Wan et al. [65] explored curcumin's role in epigenetic modulation and tumor immunity, suggesting its utility as an adjuvant in antitumor therapy. These findings underscore curcumin's versatility as a bioactive agent with significant potential across antiviral, neuroprotective, and cardioprotective domains, alongside its established anticancer and antimicrobial properties.

Synergistic Effects

The synergistic effects of curcumin and its derivatives have been extensively investigated, revealing their ability to enhance the efficacy of other therapeutic agents through complementary mechanisms. Xu et al. [66] demonstrated the synergistic action of curcumin and 5-fluorouracil in hepatocellular carcinoma, showing improved inhibition of tumor growth and offering a novel combination strategy for cancer therapy. Similarly, Targhi et al. [67] explored curcumin-Cu and curcumin-Ag nanoparticle-loaded niosomes, which exhibited enhanced antibacterial and anti-biofilm activities against resistant microbial strains. Zoi et al. [68] investigated the combined effects of curcumin and radiotherapy on glioma cells in vitro, revealing significant anti-glioma activity and improved radiation sensitivity.

Younes et al. [69] reviewed molecular mechanisms underlying curcumin's synergy with chemotherapeutic agents, highlighting its ability to inhibit cancer metastasis, invasion, and proliferation. Hosseini et al. [70] evaluated the synergistic anticancer effects of curcumin and crocin on human colorectal cancer cells, proposing a therapeutic strategy that effectively inhibits tumor growth and induces apoptosis. Ghobadi et al. [71] emphasized the potential of co-administering curcumin with other phytochemicals to improve anticancer outcomes by targeting multiple molecular pathways, enhancing the therapeutic index, and minimizing side effects.

Akyüz et al. [72] assessed the effects of combining curcumin, vitamin C, and chemotherapy drugs on MCF-7 breast cancer cells. Their findings demonstrated improved cell viability and reduced inflammation, suggesting a promising adjunctive role for curcumin in reducing the adverse effects of cancer drugs. These studies collectively highlight the potential of curcumin and its heterocyclic derivatives to synergize with other drugs, enhancing their therapeutic efficacy in cancer, microbial infections, and inflammation. By leveraging these synergistic interactions, future therapeutic approaches can be optimized to achieve better treatment outcomes with lower dosages and reduced side effects.

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