A Review on Synthesis and Biological Activity of Curcumin and Curcumin Derivatives

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Curcumin is a common polyphenolic composite and is the main chemical component of Curcuma longa linn. commonly known as turmeric. It is a well-known natural herbal herb traditionally utilized as a flavoring and coloring agent in Indian cooking. Curcumin chemically is diferuloyl methane unit [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6 heptadiene-3,5-dione] including two ferulic acid residues linked by a methylene bridge. An aromatic o-methoxy phenolic group, α,β-unsaturated β-diketo moiety and a seven carbon linker are essential for the activity. Extensive research gave proof for the role of these various functional groups in its significant biological activities. Due to physiochemical properties such as solubility, stability, bioavailability issues its use is limited in the therapy. To widen its use, various curcumin derivatives and analogs were summarized and assessed for its biological influence. The present review summarizes the different ways of synthesis of curcumin derivatives with its potential activities that are now in development for the enhancement of bioavailability and therapeutic activity.

Keywords: Curcumin; biological activity; natural and synthetic analogues for solubility enhancement.
1. INTRODUCTION

Curcuma genera has about 70 species, some medicinally important species are Curcuma xanthorrhiza, Curcuma zedoaria, Curcuma aromatica, Curcuma caesia and Curcuma amada [1]. Curcuma longa is the usual chemically examined species of Curcuma [2]. Curcumin is a common polyphenolic compound, collected from the dry rhizomes of Curcuma longa linn. Generally described as Haldi, Indian saffron, belonging to the family Zingiberaceae. Turmeric is one of nature’s most powerful healers, is used either raw or in dehydrated form for its coloring, aroma, flavoring and therapeutic properties [3]. Curcuma longa is a high perennial herb with high, broad leaves that expand straight upward from the bottom of the plant. The height of the mature plant grows upto 3 to 4 feet or tall with deep green foliage and yellow tipped flowers. The fresh, as well as dehydrated tubers, rhizome and its oil, are used medicinally [4]. Turmeric is identified as “golden spice” as well as the “spice of life” due to its various different clinical applications without any known antagonistic effects [5]. The plant is original to the South and Southeastern Asian territory, needs temperature between 20°C to 30°C [6].

Curcuma longa is a tropic rhizomatous produce farmed in India, followed by Bangladesh, China, Thailand, Cambodia, Malaysia, Indonesia, and the Philippines. In India, Tamil Nadu, Andhra Pradesh, Maharashtra, Orissa, Karnataka and Kerala are the most turmeric growing states [7].

Curcuma longa contains more than 235 compounds, primarily phenolic compounds and terpenoids including diarylheptanoids and diarylpentanoids, phenylpropene and phenolic composites, monoterpenes, sesquiterpenes, diterpenes, triterpenoids, sterols and alkaloidal composites. Curcuminoids and other curcuminoids (diarylheptanoids) and crucial oils are significant bioactive components in turmeric.

Curcuminoids comprises:

| Constituents     | Other name | %   |
|------------------|------------|-----|
| curcumin         | curcuminI  | 71.5|
| demethoxycurcumin| curcuminII | 19.4|
| bisdemethoxycurcumin| curcumin III | 9.1|

Turmeric holds an essential oil (5%), which contains a mixture of monoterpenes, sesquiterpenes and diterpenes. Main monoterpenes are p-cymene, β-phellandrene, terpinolone, and cineole. Important sesquiterpenes are Ar-turmerone, β-turmerone, and α-turmerone. Other constituents are proteins (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%), moisture (13.1%), zingiberene, curcumol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, and turmeronols [2,7,8].

2. POTENTIAL BIOLOGICAL ACTIVITY OF CURCUMINOIDS

Several experts and research workers stated a number of scientific works on pharmacological qualities of Curcuma longa and the literature survey revealed that principal investigation activities were concentrated toward curcumin and curcuminoids. Curcumin exerts a broad spectrum of pharmacological actions with variety of mechanism of actions [9-30].

![Fig. 1. Turmeric plant and dried rhizomes](image-url)
3. NATURAL ANALOGUE OF CURCUMINOIDS

Naturally, curcuminoids contain 3 major types and they only vary by the methoxy group connected to the phenolic ring - Curcumin I is dihydroxycurcumin, Curcumin-II is demethoxycurcumin (DMC) and Curcumin-III is bis-demethoxycurcumin (BDMC).

The curcumin molecule is different in its physiological impressions and have more molecular target and thus broad spectrum of physiological actions. The abundance of bioactive compounds have fundamental association with the Curcumin shown in Fig. 4 and have a pharmacophore including one aryl function with 3,4 replacement such as methoxylated phenol or catechol including ferulic acid, cinnamic acid, caffeic acid, chlorogenic acid, capsaicin, gingerol, paradol, eugenol, dibenzoylmethane, dehydrozingerone, cassumunin and yakuchinone.

From Fig. 4 the presence of ortho-methoxylated phenolic chromophore helps in distinguishing curcumin from its all natural analogue which may be desirable for antioxidant and pro-oxidant characteristics of curcumin and its analogues designing and may be due to its radical-generating or hydrogen linkage donor/acceptor properties [31].
Fig. 3. Structure of curcuminoids

Fig. 4. Natural analogues of curcumin

4. CHEMISTRY OF CURCUMIN

Curcumin chemically is diferuloyl methane molecule [1,7-bis (4-hydroxy-3- methoxyphenyl)-1,6 heptadiene-3,5-dione)] comprising two ferulic acid linked by a methylene bridge. It has three different functionalities: an aromatic o-methoxy phenolic group, α,β-unsaturated β-diketo moiety and a seven carbon linker. Precise investigation in the last two decades and Literature survey had given evidence for the use of these diverse functional groups in its significant biological actions. Fig 5 structural features shows possible site of interaction and functional groups responsible for its biological activity.
Fig. 5. Curcumin chemical structure and different functionalities

Fig. 6. Structural features involved in the binding and biological activity of curcumin

Table 1. Different functional groups and their biological activity [32,33]
Now a days new analogues are being made with structural modification in the aromatic and the diketo moiety with the help of various computer aided drug design and by studying covalent-non-covalent interactions of structural functionalities with molecular targets features to improve its physicochemical activities [32,33].

5. CHEMICAL PROPERTY AND STABILITY

The structure of compound 1 immediately undergoes keto–enol tautomerization Fig. 8. From NMR studies compound 1 is not existing in solution as the diketone (1a) but only as a blend of the fairly present (due to symmetry) enol structures (1b). NMR studies using a variety of solutions at pH 3–9 have proved that the enol tautomer (1b), rather than the diketone (1a), is the only form of the molecule present at any detectable level in solution and may leads to a planar, intramolecularly hydrogen-bonded arrangement both in solution and in powder form. Compound 1 is more structurally stable in an acidic conditions, but the equilibrium shifts to the inactive form (low/no solubility) of the molecule in parallel with declining pH.
Compound 1 diminishes by two principal pathways: solvolysis and oxidative degeneration. (A) Solvolysis under alkaline pH in buffered aqueous solvent quickly attends to many fragmentation by products which were recognized as vanillin (4), ferulic acid (5), and feruloylmethane (6), (Fig. 9). The main chemical pathway formed via Autoxidation in buffered medium produces a bicyclopentadione (7) formed in aqueous conditions. (Fig. 9) and exposure to light it gives principally Photodegradation products as vanillin (4), ferulic acid (5), ferulic aldehyde (8), and vanillic acid (9), (Fig. 9). Several solvent such as methanol, isopropanol, and chloroform leads to formation of internal cyclization product a guaiacol derivative (10), (Fig. 9) [34].

6. NEED OF SYNTHESIS OF CURCUMIN ANALOGUE

- **Poor Solubility:** Curcumin belongs to BCS class II [35], hence it shows poor solubility in aqueous formulation. There are numerous methods developed to increased its solubility such as Complexation [36], Nano-particles formulation [37] and Microencapsulation [38].
- **Poor Bioavailability:** Due to the poor solubility, it has low bioavailability when taken orally. To succeed the low oral bioavailability of curcumin, various approaches have been introduced such as complexation with cyclodextrin, conjugation with nucleosides and biopolymers [39,40].
- **Extensive Metabolic Degradation:** At higher doses, limited concentration achieved in plasma due to GIT enzymes and hence its actions like anticancer activity is limited [41,42].
- **Stability Issues:** Physicochemical properties such as alkaline degradation, autoxidation, photodegradation results in formation of degradation products as well it is easily liable for formation of complex with metals and interaction of enzymes which leads to decrease in bioavailabilty [43].

![Chemical degradation pathways of curcumin](image)

**Fig. 9. Major chemical degradation pathways of curcumin**
7. SYNTHESIS AND BIOLOGICAL ACTIVITY

Literature survey reported various substitution, modification of rings and complexation done to overcome drawbacks of pure curcumin and try to enhance its oral bioavailability, and hence increased in its biological activities. In this review article reported the data for modifications of functional groups, substitutions on aromatic ring and their impacts on pharmacological activity. Synthetic derivatives of Curcumin were synthesized by substitution of ring system, cyclization, complexation to enhance their water solubility and thus bioavailability. Structures includes in non-covalent and covalent interactions of curcumin with different biomolecules discussed below. From the literatures review substituted derivatives of curcumin have better solubility, stability and thus can be used in various antimicrobial or chemotherapy. The principal aim of this review is to study different derivatives of Curcumin to overcome its drawback i.e. low solubility, stability and poor bioavailability.

Several methods for the synthesis and pharmacological properties of substituted Curcumin reported in the literature and are reported below:

7.1 Pyrazole Based Curcumin Derivatives

Dhongade describes the synthesis of 12 new pyrazole based curcumin analogues from pyrazoly1 butanone, different aromatic or heteroaromatic aldehyde and evaluated their antibacterial activities against Gram-positive and Gram-negative bacteria as well as anticancer activity against MCF-7. Anticancer activity was determined by MTT assay method using MCF-7 Breast carcinoma cell line. For antibacterial activity the molecules 1a and 1c most effectively inhibit S. aureus and E. coli with MIC ranging within 0.4 and 0.8 μg/mL and are the most potent molecules among the tested compounds. For anticancer activity only the compound 5b showed moderate anticancer activity [44] (Fig. 10).

7.2 Aminomethyl Derivatives of Methyl-Substituted Asymmetrical Curcumin Mono-Carbonyl

Kurnia was synthesized 6 novel analogs and assessed for their anticancer activity by means of cytotoxicity and selectivity toward MCF-7, WiDr, Hela, A549, PLC/PRF/5, and Chang Liver cells lines utilizing the methyl thiazolyl tetrazolium proliferation assay method. They claimed among all synthesized derivatives 2a–2e has cytotoxic for MCF-7 cells lines where as 2b has cytotoxic on HeLa, A549, and PLC/PRF/5 cell lines. 2b and 2c showed cytotoxic against Chang Liver cells lines. 2d, 2e and 2f exhibited a strong and particular cytotoxic agent against WiDr cells lines [45] (Fig. 11).

7.3 Sulfur Containing Heterocyclic Curcumin Derivatives

Du synthesized 8 novel curcumin derivatives via claisen condensation and confirmed by 1H-NMR, FTIR and MS. Antimicrobial actions toward Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Aspergillusniger tested for MIC by using serial tube dilution method. 3a–3d effective as antimicrobial agent. Especially, the compound 4-(1,3-dithiolan-2-ylidene)-1,7-di(thiophen-2-yl)hepta-1,6-diene-3,5-dione (3c) has the highest antimicrobial activity. The result shows these derivatives much better than curcumin [46] (Fig. 12).

![Fig. 10. Pyrazole based Curcumin derivatives](image-url)
7.4 Curcuminpyrazole Derivatives

Chandrashekariah synthesised pyrazole derivatives (4a & 4b) the structures confirmed by 1H and 13C NMR, LC-MS and derivatives assessed for antioxidant action (DPPH method, Superoxide anion radical scavenging assay, Nitric oxide Scavenging method) and anticancer activity on three different cell lines, MCF-7, HeLa and K-562 by using MTT assay and Tryptan blue dye exclusion assay. The compound 4a possess promising in-vitro anticancer and antioxidant activity than natural curcumin. Compound 4,4'-(1E,1'E)-2,2'(1-(4-chlorophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl)bis(2-methoxy phenol) (4a) could be a promising cost-effective drug active at non-toxic doses [47] (Fig. 13).
7.5 Cyclotriphosphazenes Containing Monocarbonyl-curcumin analogs

Seker synthesized 6 new linked structure cyclotriphosphazenes (5a-5f) from the reactions of arylxycyclotriphosphazenes and each compound was identified by using elemental analysis, FTIR, MS, NMR (1H and 31P). The synthesized compounds assessed for in vitro antimicrobial properties against Escherichia coli ATCC 8739, Staphylococcus aureus ATCC 29213, Bacillus subtilis ATCC 6633, Bacillus cereus DSMZ 4312 and Candida albicans ATCC 10231. MIC of compound 5a and 5b evaluated and it influenced against Gram-positive bacteria B. cereus and B. Subtilis. 5b and 5a was the most effective derivative with 52% and 48% inhibition rate, respectively compared to cloramphenicol against B. Subtilis. According to B. cereus with 40% and 36% inhibition rate, respectively. Antibacterial features are due to the molecules have two domain within two aromatic or Michael acceptor and two cyclotriphosphazene rings with aromatic rings within unsaturated C=C bonds flanking the carbonyl groups [48] (Fig. 14).

**Fig. 13. Curcumin pyrazole derivatives**

**Fig. 14. Cyclotriphosphazene Curcumin analog**
7.6 Novel Monofunctionalized Curcumin Derivatives as Strong Inhibitors of Inflammation and Amyloid-β Aggregation in Alzheimer’s Disease

Johant synthesized 9 curcumin derivatives (6a-6i) by etherification and esterification reactions and evaluated for anti-inflammatory, cytotoxicity by MTT assay and Thioflavin T assay. Among all synthesized curcumin derivatives Compound 6a were synthesized by etherification reactions whereas as compounds 6b, 6c and 6d were synthesized by esterification. Compound 6a, 6b & 6d exhibited more potent anti-inflammatory activity while compound 6f exhibited similar activity to curcumin. Compound 6b showed a strong anti-aggregation effect more chief than curcumin. Compound 6a, 6b, 6c, 6d and 6e showed in vitro anti-aggregation activity. They conclude that monofunctionalized curcumin derivatives gave more beneficial bioactivity than difunctionalized compound and presence of heavy groups decreased bioactivity of curcumin derivatives. Novel curcumin derivatives 6a, 6b, 6c & 6d have possible as healing compounds for treatment of AD [49] (Fig. 15).

7.7 Synthesis of Symmetrical 1,5-diphenyl-1,4-pentadien-3-one Derivatives of Curcumin

Gansynthesized a series of 1,5-diphenyl-1,4-pentadien-3-one derivatives as curcumin analogs and assessed as amyloid imaging agents. The binding affinities to Aβ plaques studied by using AD human brain homogenates and Fluorescent staining showed compound 7a clearly stained Aβ plaques inside AD brain areas. In biodistribution, radioiodinated ligand [125I]7a showed huge brain uptake and positive removal from the brain. Autoradiography in vitro additional validated the high affinities of [125I]7a. The outcomes firmly recommended that [125I]7a might be developed into potential amyloid imaging agent for the detection of senile plaques in AD. The SAR of structure shows that replacement of the substituent of phenyl ring with 4-NO2 group or any electron withdrawing group succeeded in a steep reduction in the binding affection. Hence they was proved that the phenyl rings should be electron rich in order to posses high binding affections so that it will shows stronger π-π stacking with amyloid peptides [50] (Fig. 16).

![Monofunctionalized Curcumin derivatives](image-url)
7.8 Biological Evaluation of New Curcumin–Pyrazole–Mannich Derivative Working toward Drug-Resistant Mycobacterium Tuberculosis

Singh synthesized 21 curcumin derivatives by converting Curcumin to its isoxazoles, pyrazoles, Knoevenagel condensation and their 2-(4-chlorophenoxy)-2-methylpropanoyl esters/Mannich bases. The synthesized derivatives evaluated for bio-evaluation, static/cidal activity, synergy with front-line antituberculosis drugs. Also its efficacy studied by using murine model of M. tuberculosis infection. Among them 8a dihydrochloride derivative was found to be concentration-dependent bactericidal and have potent activity against M. tuberculosis H37Rv (MIC 2µg/ml). It also shows efficacy towards drug-resistant strains and have synergistic actions with front-line antituberculosis drugs. 8a dihydrochloride required 13-times less concentration (35.6 vs 490 µmol/kg) than Ethambutol. Also it reported that the 8a acts by dual mechanism by targeting both host and microbe. It is inactive against non-mycobacterial strains as well as free from cross-resistance with existing drug resistance mechanisms [51] (Fig. 17).

7.9 New Functionalized Cyclohexene Derivatives of Curcumin

Bhuvaneswarisynthesized cyclohexene derivatives of curcuminby using one-pot multicomponent dual Michael addition strategy. The synthesized derivatives evaluated for antitumor activity MTT assay method using human breast cancer MCF-7. Among all 24 synthesized compounds (E)-4,4′,5′-trihydroxy-6′-(3-(4-hydroxy-3-methoxyphenyl)acryloyl)-3′,3′,4′-dimethoxy-3,4’-dihydro-[ 1, 1′:3′, 1′′-terphenyl]-2′,2′(1′H)-dicarbonitrile (9a) and (E)-ethyl 2′-cyano-4′′,5′ dihydroxy-6′-(3-(4-hydroxy-3-methoxyphenyl) acryloyl)-3′′-methoxy-4-methyl 1′,2′,3′,4′-tetrahydro- [1,1′:3′, 1′′-terphenyl]-2′-carboxylate (9b) examined for in-vitro anticancer actions on human breast cancer cells (MCF-7) and human normal breast cells (HBL 100). The obtained data showed that the powerful cytotoxicity on MCF-7 cells and more limited cytotoxicity on HBL 100 cells than simple curcumin. Also the molecular docking studies of synthesizes compound helped to rationalize anti-apoptotic Bcl-2 binding activity. The docking Study of compounds 9a & 9b with Bcl-2 was seen to be more efficient activity than purified curcumin. The compound 9b shows higher potency towards cytotoxic action at 10 mM/mL against human breast cancer cells (MCF-7 as compared with pure curcumin). Thus they concluded that the introduction of functionalized cyclohexene moiety in curcumin may enhance the cytotoxic activity [52] (Fig. 18).

7.10 Synthesis of Dimethylaminocurcuminoid Derivatives

Bhanupriya synthesized9 dimethylaminocurcuminoid derivatives by aldol condensation. Three different series such as 4-phenylaminomethyl curcumin, aryldenicurcin and pyrazolecurcumin derivatives synthesized. The all synthesized molecules evaluated for In-vitro anti-inflammatory, antioxidant (DPPH, H2O2 scavenging process) and antibacterial actions. Amongs all Synthesized dimethylaminocurcuminoid derivatives evaluated for antibacterial activity against Gram positive Staphylococcus aureus (ATCC 25923) and Gram negative such as Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Klebsiella pneumonia (ATCC 13883) bacteria via the zone of inhibition system and compound 10a, 10d, 10f, 10g and 10h showed...
moderate to good antibacterial activity against E. coli. The compound 10c, 10d, 10g and 10h showed strong anti-inflammatory characteristics than pure curcumin. The structural data showed that the replacement of or substitution of β-diketone by pyrazole/phenylaminomethylcurcumin/arylidienecurcumin groups helped to improves the biological qualities as compared with pure Curcumin. Compound 10d, 10e, 10f and 10h scavenging activity is moderate by DPPH method, 10a and 10d showed potent where as comp 10b, 10e, 10f and 10h showed moderate H2O2 scavenging activity resembled to curcumin and ascorbic acid. Also Molecular docking studies shows that they has very good cyclooxygenase inhibition activity [53] (Fig. 19).

### 7.11 Synthesis of Phosphorylated, Etherified, and Esterified Derivatives of Curcumin

Ding synthesized 18 compound by phosphorylated, etherified, and esterified curcumin derivatives. Different derivatives synthesized by introduction of hydrophilic groups and evaluated for antitumor cell line growth actions toward three tumor cell lines by MTT assay. Introduction of nitrogen polar groups in compound 11b enhanced solubility in H2O and stability in plasma. Out of all synthesized derivatives Compound 11a, 11b, 11c displayed more effective antitumor cell line growth actions against HeLa cells, where as compound 11d showed higher antitumor cell line growth activity on MCF-7 cells than curcumin [54] (Fig. 20).

#### Fig. 17. Pyrazole-mannich derivatives of Curcumin

#### Fig. 18. Cyclone cyclohexene derivatives of Curcumin
Fig. 19. Dimethylamino Curcuminoid derivatives

Fig. 20. Phosphorylated, etherified and esterified derivatives of Curcumin
8. CONCLUSION

Present review article highlights the recent researches on curcumin to overcome its drawbacks. Recent literature review reveals that the curcumin and its derivatives can be used for broad spectrum of action. Its various derivatives synthesized by different chemical reaction as well as further evaluated for antioxidant, antimicrobial, anti-alzheimer, anticancer activity. The biological evaluation data shows the better potency of curcumin derivatives/analogs as compare to pure curcumin itself. This review article can motivate interested researcher for further continuous development of curcumin derivatives by various reaction and also for explore the biological actions by various testing. The data suggested that those derivatives are excellent template needed for elucidation, designing and further development of molecules so that researchers will overcome drawbacks of pure curcumin.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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