Asian Journal of Chemical Sciences

10(4): 7-23, 2021; Article no.AJOCS.75758
ISSN: 2456-7795

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

RinaIkhar[1*], Prafulla Sabale[1] and Pravin Kadam[1]

[1]Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, India.

Authors' contributions

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

Article Information

DOI: 10.9734/AJOCS/2021/v10i419099
Editor(s):
(1) Dr. SungCheal Moon, Korea Institute of Materials Science, Korea.
Reviewers:
(1) Martin, Artois University, France.
(2) Chukwu, Chukwuma Joseph, Alex Ekwueme Federal University, Nigeria.
Complete Peer review History: https://www.sdiarticle4.com/review-history/75758

Review Article

Received 11 August 2021
Accepted 23 October 2021
Published 30 October 2021

ABSTRACT

Curcumin is a common polyphenolic composite and is the main chemical component of Curcuma longa linn.commonlyknown 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 summarisesthe 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.

**Corresponding author: E-mail: rinaikhar23@gmail.com;*

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 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. Curcumins 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-phellandrane, 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, curcumenol, 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

Fig. 2. Potential biological activities of curcuminoids

3. NATURAL ANALOGUE OF CURCUMINOIDS

Naturally, curcuminoids contains 3 major types and they only vary by the methoxy group connected to the phenolic ring - Curcumin I is dihydroxycurcumin, Curcumin-II isdemethoxycurcumin (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 apharmacophore 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, cassumuin 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].

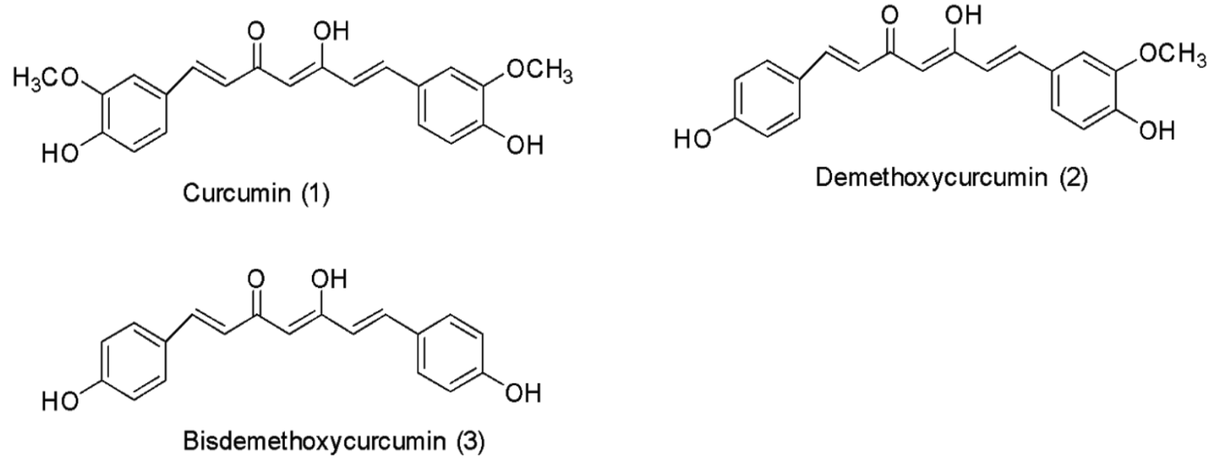


Fig. 3. Structure of curcuminoids

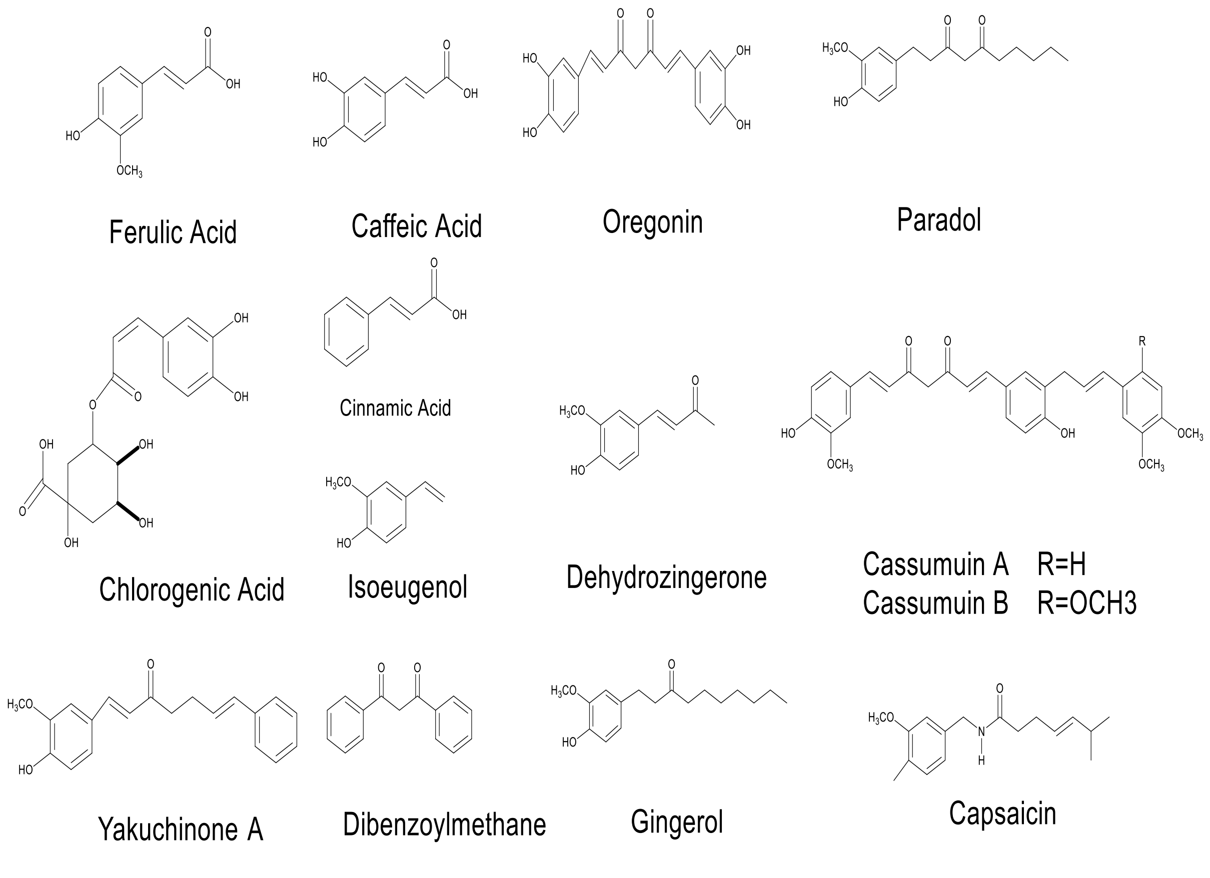


Fig. 4. Natural analogues of curcumin

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.

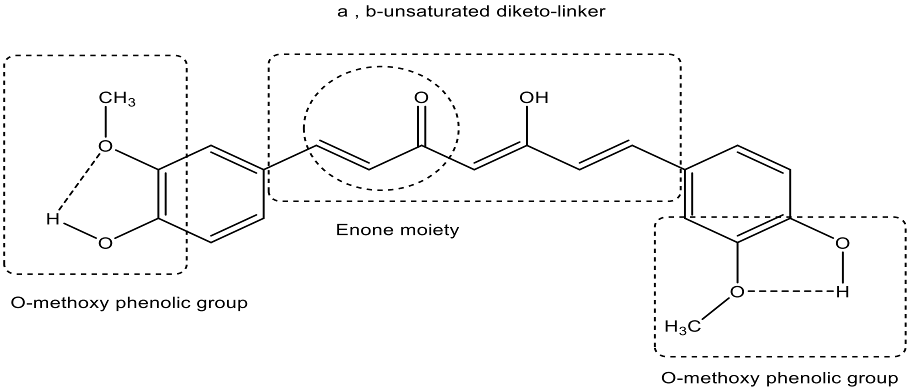


Fig. 5. Curcumin chemical structure and different functionalities

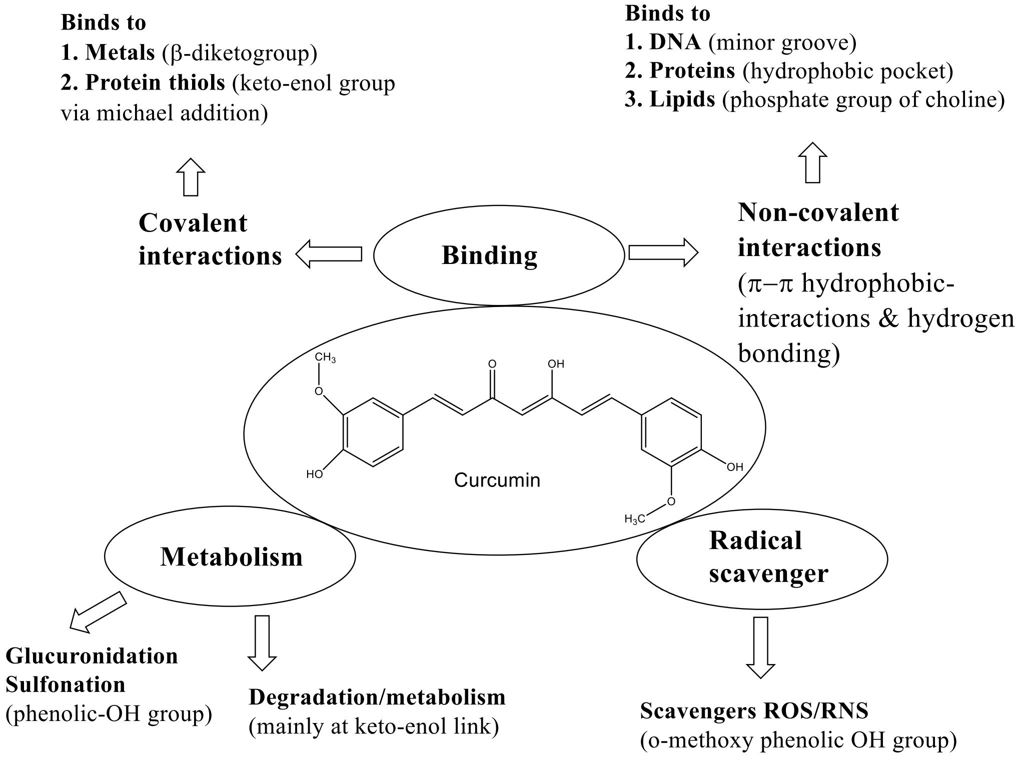


Fig. 6. Structural features involved in the binding and biological activity of curcumin

Table 1. Different functional groups and their biological activity [32,33]

Functional group	Activity
o-methoxy phenolic OH groups	ROS scavenging activities
α,β-unsaturated keto-enol structure	antitumor activity
phenolic OH groups	anticancer activity
removal of o-methoxy groups	antitubercular activity
substitutions of OH group on aromatic ring	anticancer activity
non-covalent interactions	binding to various biomolecules, and such interactions can cause reversible alterations in the curcumin biology
covalent interactions	Interaction with metals and any protein thiols can generate unchangeable differences in its biological function.

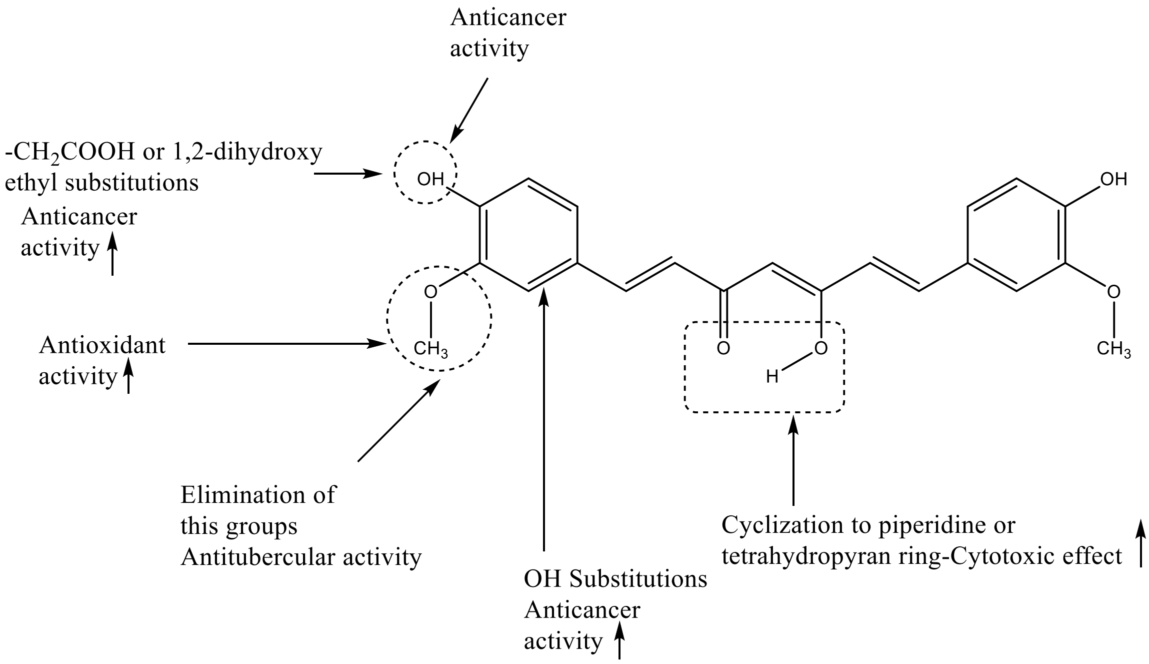


Fig. 7. Structure-activity relationships of curcumin analogs

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−enoltautomerization 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.

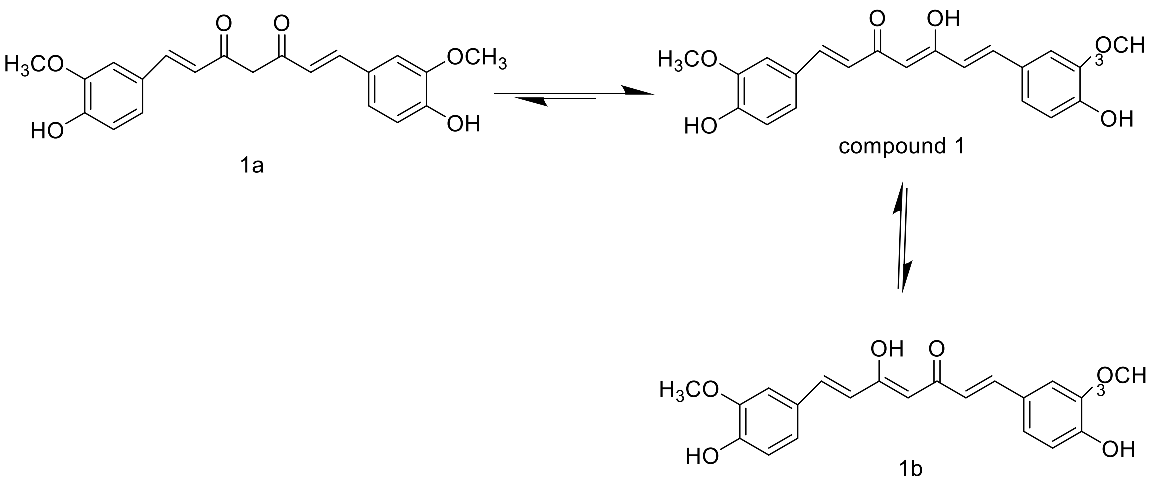


Fig. 8. Tautomerization of curcumin

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 Bioavailabilty:** Due to the poor solubility, it has low bioavailabilty 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].

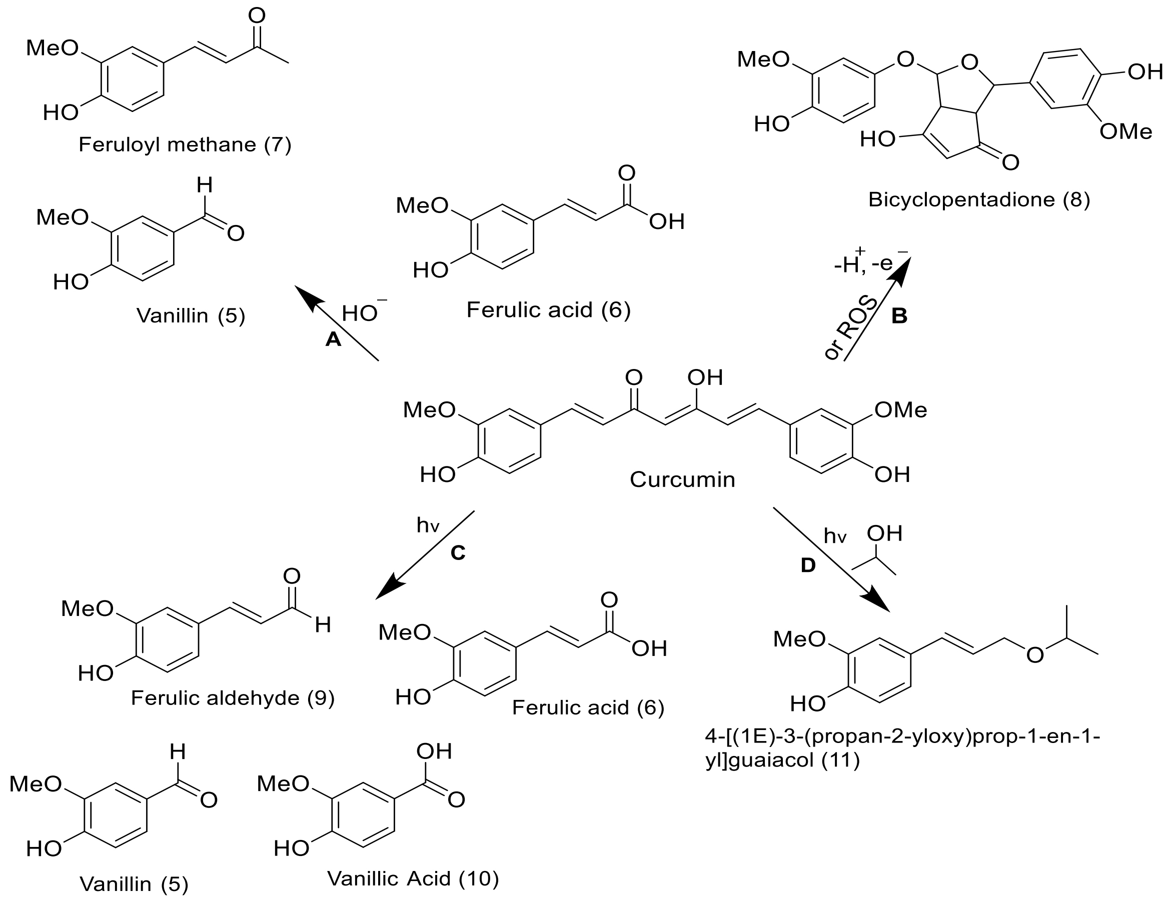


Fig. 9. Major chemical degradation pathways of curcumin

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 bioavailabilty, 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

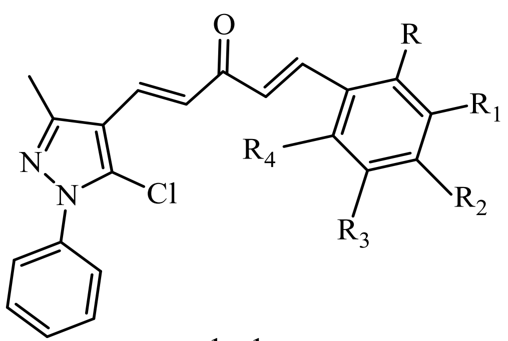
Dhongade describes the synthesis of 12 new pyrazole based curcumin analogues from pyrazolyl butanone, different aromatic or heteroaromatic aldehyde and evaluated their antibacterial activities against Gram-positive and Gram-negative bacteria as well as anticancer activity against MCF-7. Anticancer activity 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 amongs 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).



1a-1c

Compound Code	Nature of R group				
	R	R^1	R^2	R^3	R^4
1a	H	H	-OH	H	H
1b	$-OCH_3$	H	$-OCH_3$	H	$-OCH_3$
1c	2-Napthaldehyde				

Fig. 10. Pyrazole based Curcumin derivatives

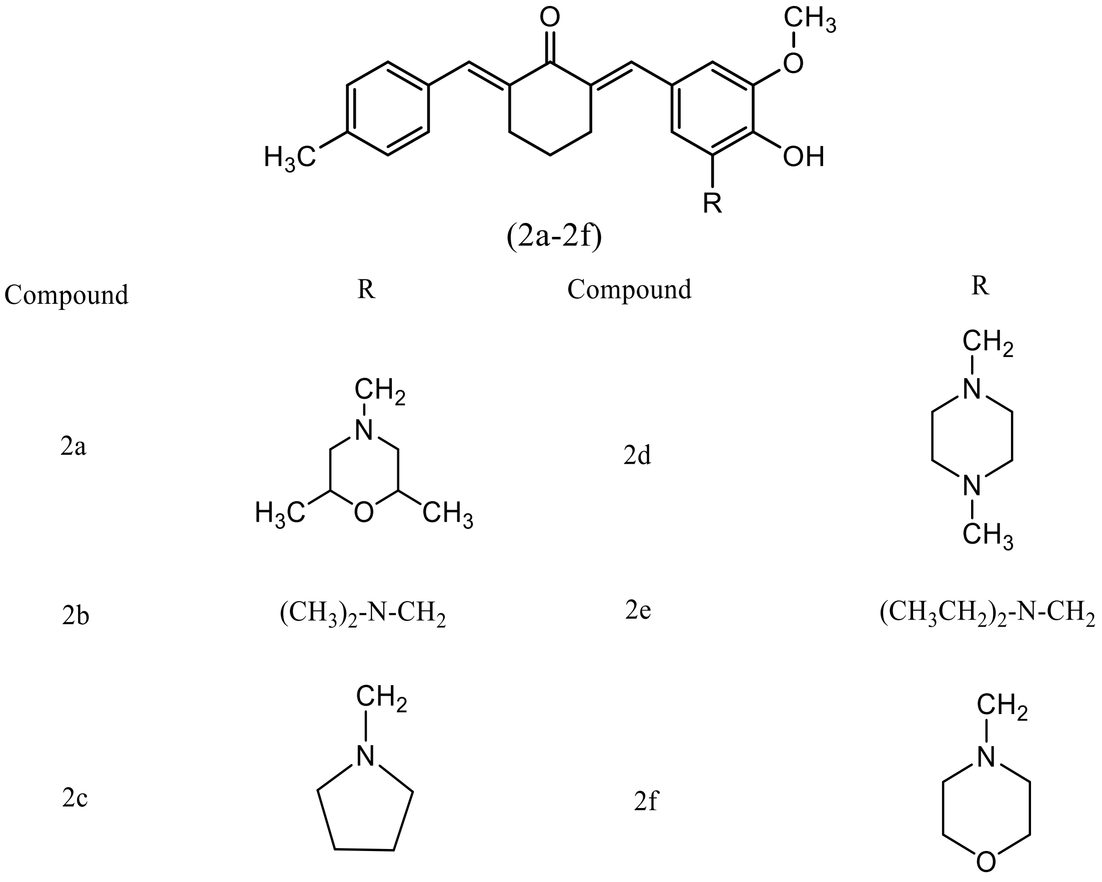


Fig. 11. Aminomethyl derivatives of curcumin

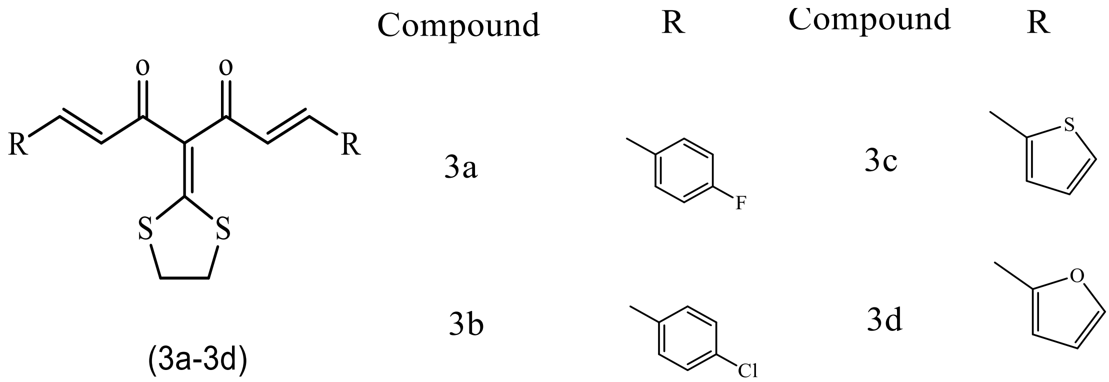
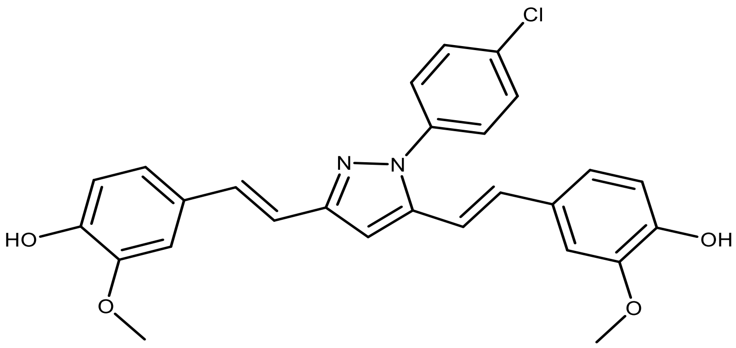


Fig. 12. Sulfur containing Curcumin derivatives

7.4 Curcuminpyrazole Derivatives

Chandrashekariah synthesisedpyrazole 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).

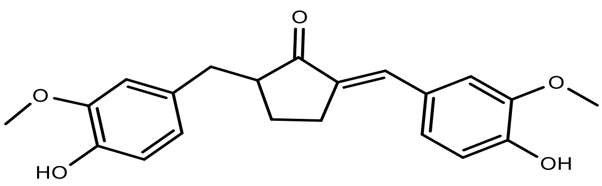


(4a)

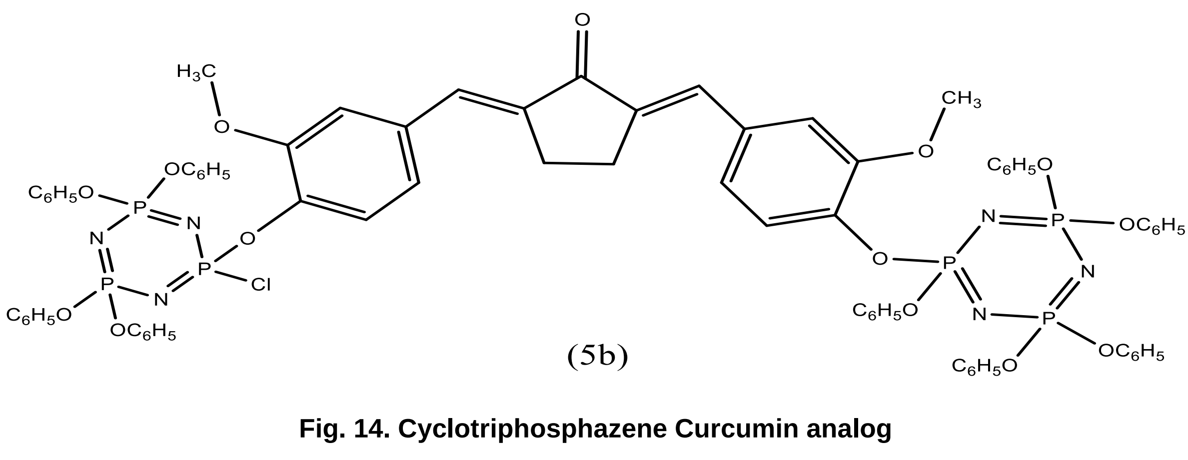
Fig. 13. Curcumin pyrazole derivatives

7.5 Cyclotriphosphazenes Containing Monocarbonylcurcuminanalogs

Seker synthesized 6 new linked structure cyclotriphosphazenes (5a-5f) from the reactions of aryloxycyclotriphosphazenes 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. Substilis. **5b** and **5a** was the most effective derivative with 52% and 48% inhibition rate, respectively compared to cloramphenicol against B. Substilis. 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).



(5a)



(5b)

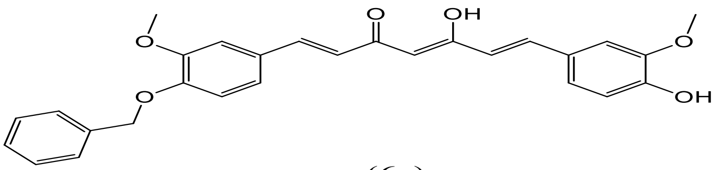
Fig. 14. Cyclotriphosphazene Curcumin analog

7.6 Novel Monofunctionalized Curcumin Derivatives as Strong Inhibitors of Inflammation and Amyloid-β Aggregation in Alzheimer's Disease

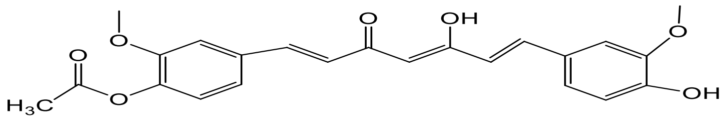
Johant synthesized 9 curcumin derivatives (6a-6i) by etherification and esterification reactions and evaluated for anti-inflammatory, cytotoxicity by MTT assay and Thioflavin T assay. Amongs all synthesized curcumin derivatives Compound 6a were synthesized by etherification reactions where as compounds 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

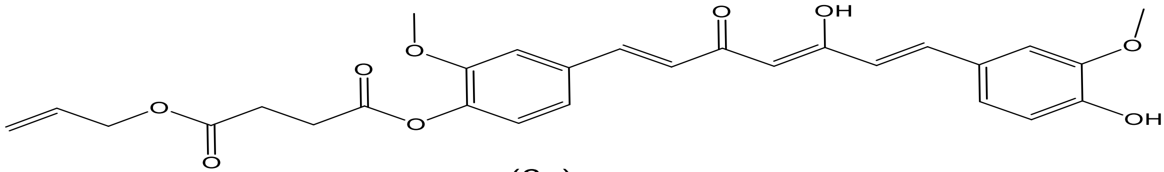
Gansynthesized a series of 1,5-diphenyl-1,4-pentadien-3-one derivatives as curcuminanalogsand assessed as amyloid imaging agents. The binding affinities to Aβ plaques studied by using AD human brain homogenates and Fluorescent staining showed compound **7a** clearly stained Aβ plaques inside AD brain 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).



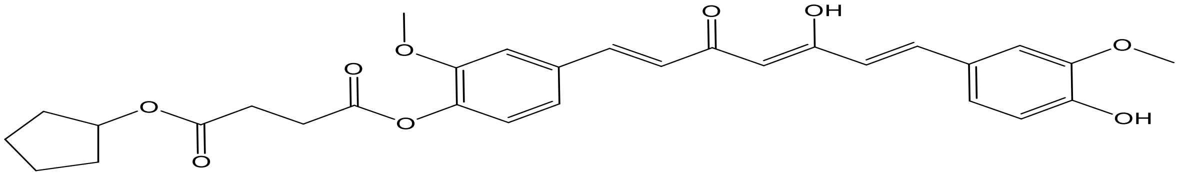
(6a)



(6b)

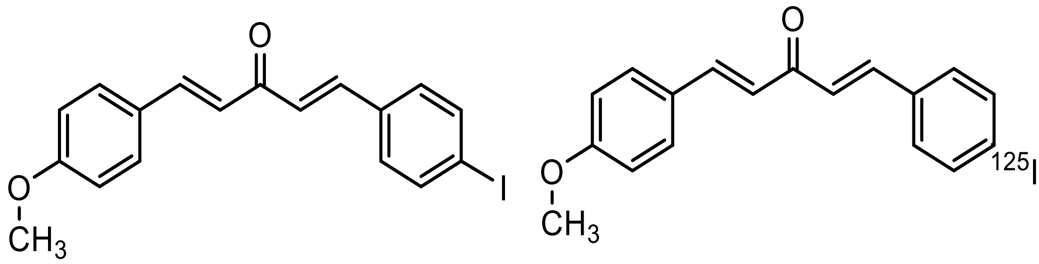


(6c)



(6d)

Fig. 15. Monofunctionalized Curcumin derivatives



7a [^{125}I] 7a

Fig. 16. 1,5- diphenyl-1,4-pentadien-3-one derivatives of Curcumin

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/cidality, synergy with front-line antituberculosis drugs. Also its efficacy studied by using murine model of M. tuberculosis infection. Amongs 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

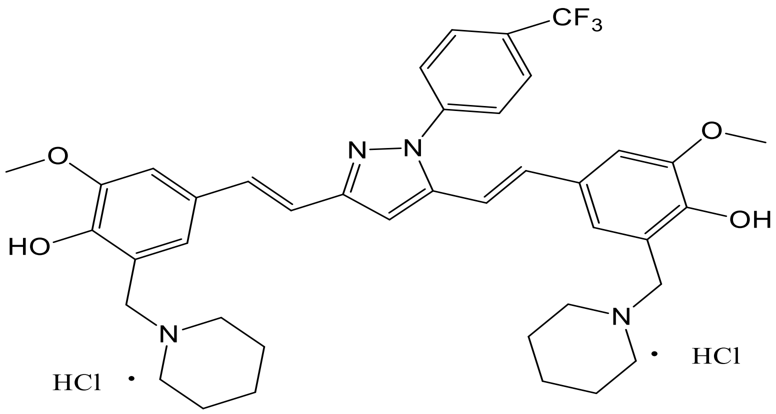
Bhuvaneswarisynthesized cyclohexene derivatives of curcuminby using one-pot multicomponent dual Michael addition strategy. The synthesized derivatives evaluated for antitumor activity MTT assay method using human breast cancer MCF-7. Amongs all 24 synthesized compounds (E)-4,4'',5'-trihydroxy-6'-(3-(4- hydroxy-3-methoxyphenyl)acryloyl)-3,3''-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, arylidenecurcumin and pyrazolecurcumin derivatives synthesized. The all synthesized molecules evaluated for In-vitro anti-inflammatory, antioxidant (DPPH , H_2O_2 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).

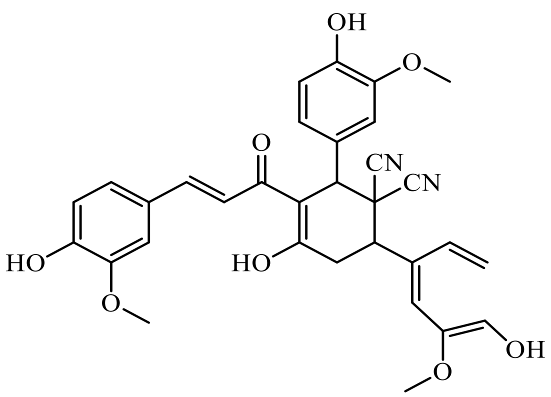
7.11 Synthesis of Phosphorylated, Etherified, and Esterified Derivatives of Curcumin

Ding synthesized 18compound 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 H_2O 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).

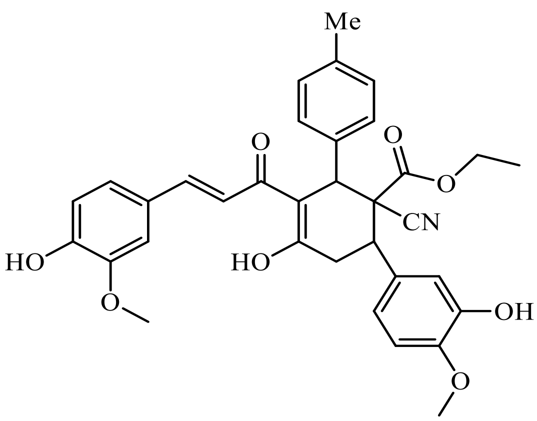


8a

Fig. 17. Pyrazole-mannich derivatives of Curcumin

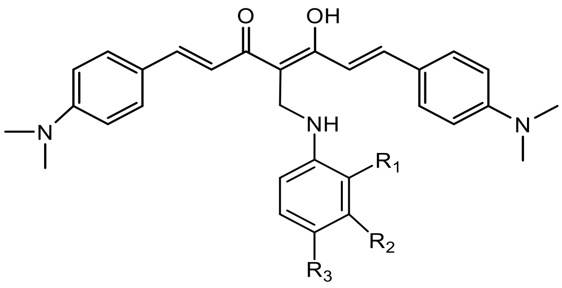


(9a)



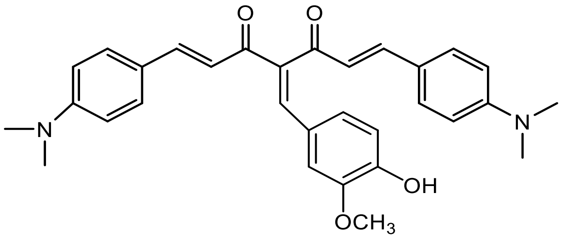
(9b)

Fig. 18. Cyclone cyclohexene derivatives of Curcumin

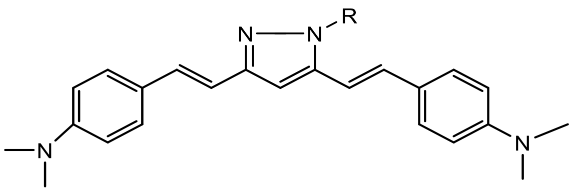


comp.	R^1	R^2	R^3
10a	H	H	F
10b	H	CF_3	H
10c	OCH_3	H	H

(10a-10c)

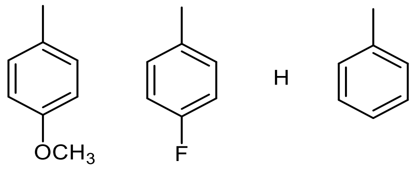


(10d)



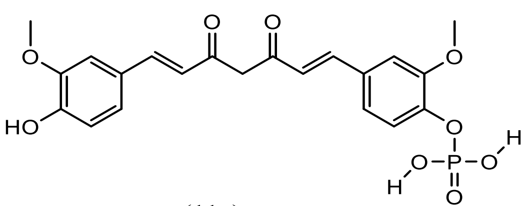
(10e-10h)

R=

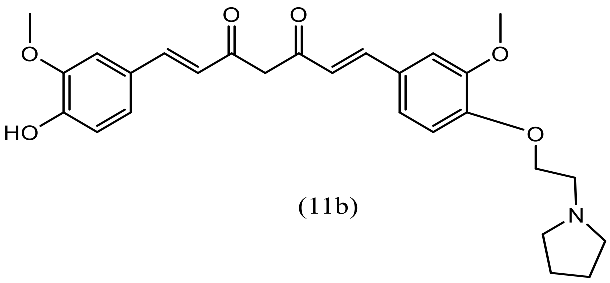


(10e) (10f) (10g) (10h)

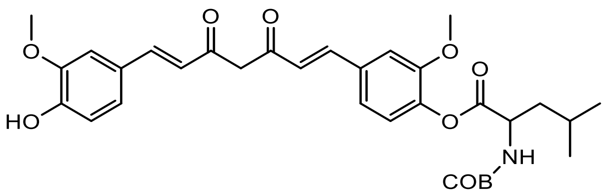
Fig. 19. Dimethylamino Curcuminoid derivatives



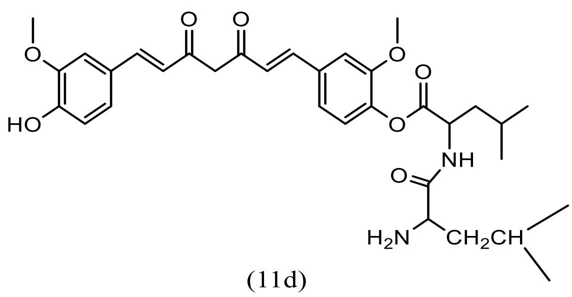
(11a)



(11b)



(11c)



(11d)

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-alzeimer, anticancer activity. The biological evaluation data shows the better potency of curcumin derivatives/analog as compare to pure curcumin itself. Thisreview 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.

REFERENCES

1. Duggi S, Handral HK, Handral R, Tulsianand G, Shruthi SD. Turmeric: Nature's precious medicine.6thed.vol.3. Asian Journal of Pharmaceutical and Clinical Research. 2013;10-16.
2. Li S, Yuan W, Deng G, Wang P, Yang P,Aggarwal BB. Chemical composition and product quality control of turmeric (*Curcuma longa* L.). 2nd ed. Pharm Crops. 2011;28-54.
3. Dhanya R, Mishra BB, Khaleel KM. Effect of gamma irradiation on curcuminoids and volatile oils of fresh turmeric (*Curcuma longa*). Radiat Phys Chem. 2011;80:1247–1249.
4. Zhu ZY. Flora Sichuanica. Sichuan Nationalities Publishing House. 1992;604-610.
5. Roopadarshini V, Gayatri MC. Isolation of somaclonal variants for morphological andbiochemical traits in *Curcuma longa* (turmeric). 2nd ed. Res Plant Biol. 2012;31-37.
6. Gilani AHT, Shah AJ, Ghayur MN, Majeed K. Pharmacological basis for the use of turmeric in gastrointestinal and respiratory disorders. Life Sci. 2005;76:3089–3105.
7. Sabale P, Modi A, Sabale V, *Curcuma longa* Linn. A phytochemical and phytopharmacological review. 5th ed. vol.2. Research Journal of Pharmacognosy and Phytochemistr. 2013;59-68.
8. Bagchi A. Extraction of curcumin. 1st ed. J Envt Sci Toxicol Food Tech. 2012;1-16.
9. Yue GGL, Chan BCL, Hon PM, Lee MYH,Fung KP, Leung PC, Lau CBS. Evaluation of *in vitro* anti-proliferative and immunomodulatory activities of compounds isolated from *Curcuma longa*. Food Chem Toxicol. 2010;48:2011-2020.
10. Chandru H, Sharada AC, Bettadaiah BK, Ananda Kumar CS, Rangappa KS, Sunila, Jayashree K. In vivo growth inhibitory and anti-angiogenic effects of synthetic novel dienonecyclopropoxycurcumin analogs on mouse Ehrlich ascites tumor; 15th ed. Bioorg Med Chem. 2007;7696–7703.
11. Yuan X, Li H, Bai H, Su Z, Xiang Q, Wang C, Zhao B, Zhang Y, Zhang Q, Chu Y, Huang Y. Synthesis of novel curcumin analogues for inhibition of 11β-hydroxysteroid dehydrogenase type 1 with anti-diabetic properties. Eur J Med Chem. 2014;77:223-230.
12. Fang L, Gou S, Liu X, Cao F, Cheng L. Design, synthesis and anti-Alzheimer properties of dimethylaminomethyl-substituted curcumin derivatives.24th ed. Bioorg Med Chem Lett. 2014;40–43.
13. Maher P, Akaishi T, Schubert D, Abe KA. pyrazole derivative of curcumin enhances memory. 31st ed. Neurobiol Aging. 2010;706–709.
14. Ahn CM, Park BG, Woo HB, Ham J, Shin WS, Lee S. Synthesis of sulfonyl curcumin mimics exerting a vasodilatation effect on the basilar artery of rabbits. 19th ed. Bioorg Med ChemLett. 2009;1481–1483.
15. Sahu PK, Gupta SK, Thavaselvam D, Agarwal DD. Synthesis and evaluation of antimicrobial activity of 4H-pyrimido[2,1-β] benzothiazole, pyrazole and benzylidene derivatives ofcurcumin. Eur J Med Chem. 2012;54:366-378.
16. Bhardwaj S, Khatik GL, Kaur P, Nayak SK. Computer aided drug design through molecular docking: Identification of selective COX-2 inhibitors as potential NSAID's.11th ed. Journal of Pharmacy Research. 2017;6:604-608.
17. Yusuf SA, Sada I, Yusuf H, Olomola OT, Adeyemi MC Ajibade OS. Synthesis, Antimalarial activity and Docking Studies of Monocarbonyl Analogues of Curcumin.

29th ed. Ovidius University Annals of Chemistry. 2018;92-96.

18. Banupriya G, Sribalan R, Padmini V, Shanmugaiah V, Biological Evaluation and Molecular Docking Studies of new curcuminoid derivatives: Synthesis and Characterization. 26th ed. Bioorg and Med Chem. Lett. 2016;7:1655-1659.
19. Singh R, Mehta A, Mehta p, Shukla K. Anthelmintic activity of rhizome extract of Curcuma longa and Zingiberofficinale (Zingiberaceae)3rd ed. Int J Pharm Pharmsci. 2011;2:236-237.
20. Kohli K, Ali J, Ansari MJ, Raheman Z.Curcumin: a natural antiinflammatory agent. 3rd ed. vol 37. Indian Journal of Pharmacology; 2005.
21. Futagami Y. Antiallergenic activity of extracts from Curcuma longa, effect of curcuminoids. 13th ed.Wakanlyakugaku Zsshi; 1996. page no.430–431.
22. Braga ME, Leal PF, Carvalho JE,Meireles MA. Comparison of yield, composition, and antioxidant activity of turmeric (*Curcuma longa* L.) extracts obtained using various techniques.22nd ed. vol.51. J Agric Food Chem;2003. page no.6604-6611.
23. Lee HS. Antiplatelet property of Curcuma longa L. rhizome-derived ar-turmerone. 12th ed. BioresourTechnol. 2006;97:1372-1376.
24. Tushar, Basak S, Sarma GC, Rangan L. Ethnomedical uses of Zingiberaceous plants of Northeast India.1st ed. J Ethnopharmacol. 2010;132:286-296.
25. Srinivas K, Sambaiah K. The effect of spices on cholesterol 7 α hydroxylase activity on serum & hepatic cholesterol level in rat. Internatl. J VitNutri Res. 1991;61:364–369.
26. Singh G, Singh OP, Maurya S. Chemical and biocidal investigations on essential oils of some Indian Curcuma species;1st ed. Prog Cryst Growth Charact Mat. 2002;45:75-81.
27. Van Dau N, Ham NN, Khac DH, Lam NT, Son PT, Tan NT, et al. The effects of a traditional drug, turmeric (*Curcuma longa*), and placebo on the healing of duodenal ulcer. 1st ed. Phytomedicine. 1998;5:29-34.
28. Bala K, Tripathy BC, Sharma D.Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions 7th ed. Biogerontology. 2006;81–89.
29. Ramos A, Visozo A, Piloto J, García A, Rodríguez CA,Rivero R. Screening of antimutagenicity via antioxidant activity in Cuban medicinal plants. J Ethnopharmacol. 2000;87:241-246.
30. Cohly HHP, Asad S, Das SK, Angel MF,Rao M. Effect of antioxidant (turmeric, turmerin and curcumin) on human immunodeficiency virus. 4th ed. Int J Mol Sci. 2003;22–33.
31. Curcumin and its biological importance. Chapter 1. Curcumin and its derivatives as Antioxidants and DNA Intercalators.
32. Priyadarshini I. Chemical and structural features influencing the biological activity of curcumin. Current Pharmaceutical Design. 2013;19:2093-2100.
33. Arshad L, Haque MA, BhukhariSNA, Jantan I. An overview of structure-activity relationship studies of curcumin analogs as antioxidant and anti-inflammatory agents. Future Med.Chem; 2017.
34. Nelson KM, Dahlin JL, Bisson J, Pauli GF, Walters MA. The essential medicinal chemistry of curcumin. J. Med. Chem. 2017;60:1620-1637.
35. Hu L, Shi Y, Li JH, Gao N, Ji J, Niu F, Chen Q, Yang X, Wang S. Enhancement of oral bioavailability of curcumin by a novel solid dispersion system. 6th ed. Aaps Pharm sci tech. 2015;16:1327-1334.
36. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK.Curcumin–phospholipid complex: preparation, therapeutic evaluation and pharmacokinetic study in rats. 1st ed. International Journal of Pharmaceutics. 2007;330:155-163.
37. Thangapazham RL, Puri A, Tele S, Blumenthal R, Maheshwari RK. Evaluation of a nanotechnology-based carrier for delivery of curcumin in prostate cancer cells. 5th ed. vol.32. International journal of oncology. 2008;1119-1123.
38. Mohanty C, Sahoo SK. The *in vitro* stability and *in vivo* pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation. 25th ed. Biomaterials. 2010;31: 6597-6611.
39. Gupta KR, Pounikar AR, Jaiswal PM. Formulation and Evaluation of Hydrotropic Solid Dispersions of Curcumin. 1st ed. J. Curr. Chem. Pharm. Sci. 2019; 9.
40. Tonnesen HH, Masson M, Loftsson T. Studies of curcumin and curcuminoids, Cyclodextrin complexation: solubility, chemical and photochemical stability. 1st ed. vol.244. International Journal of Pharmaceutics. 2002;127-135.

41. Lopez-Lazaro M. Anticancer and carcinogenic properties of curcumin: Considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. S1 ed. Molecular Nutrition & Food Research. 2008;52:S103-S127.
42. Aggarwal BB, Surh YJ, Shishodia S. The molecular targets and therapeutic uses of curcumin in health and disease. Springer Science & Business Media; 2007.
43. Kumar S, Narain U, Tripathi S, Misra K. Synthesis of curcumin using nanotechnology. Journal of Food Science; 2010.
44. Dhongade SR, Chougale UB, Chavan HV, Deshmukh SM. Synthesis and biological evaluation of pyrazole based curcumin analogues as promising antimicrobial and anticancer agents.2nd ed. RJLBPCS. 2019;5:1164-1175.
45. Kurnia A, Saputri FC, Hayun H. Synthesis and anticancer potential of aminomethyl derivatives of methyl-substituted asymmetrical curcumin mono-carbonyl. 8th ed. Journal of Applied Pharmaceutical Science. 2019;9:018-24.
46. Du H, Wang D, Lyu H, Cai L, Wang D. Synthesis and Antimicrobial Activities of Containing Sulfur Heterocyclic Curcumin Derivatives. 1st ed. Journal of Biology Engineering and Medicine. 2020;1:1-3.
47. Chadrashekariah SA, Puneeth HR. A study on synthesis and biological evaluation of curcumin pyrazole derivatives for anticancer and antioxidant properties. 8th ed. JETIR. 2018;5:594-601.
48. Seker MG, Akbal T, Atilla D, Avsar N, Ibisoglu H. Synthesis and antimicrobial effects of cyclotriphosphazenes containing monocarbonylcurcumin analogs. 4th ed. Marmara Pharma J. 2018;22:536-546.
49. Johant LB, Yisett G, Deborah D, Stephens DE, Ricardo S, Enrique M, Marcelino G, Fernandez PL, Rao KS, Larionov OV, Durant-archibold AA. Assessment of novel curcumin derivatives as potent inhibitors of inflammation and amyloid-β aggregation in Alzheimer’s disease. S1 ed. Journal of Alzheimer's Disease. 2017;60:1-10.
50. Gan C, Hu J, Nan DD, Wang S, Li H. Synthesis and biological evaluation of curcumin analogs as β-amyloid imaging agents. 9th ed. Future Medicinal Chemistry. 2017;14:1587-1596.
51. Singh AK, Yadav P, Karaulia P, Singh VK, Gupta P, Puttrevu SK, et al. Biological evaluation of novel curcumin–pyrazole–mannich derivative active against drug-resistant Mycobacterium tuberculosis. 12th ed. Future Microbiology. 2017;15:1349-1362.
52. Bhuvaneswari K, Sivaguru P, Lalitha A. Synthesis, Biological Evaluation and Molecular Docking of Novel Curcumin Derivatives as Bcl-2 Inhibitors Targeting Human Breast Cancer MCF-7 Cells. 2nd ed. Chemistry Select. 2017;35:11552-11560.
53. Banuppriya G, Sribalan R, Padmini V, Shanmugaiah V. Biological evaluation and molecular docking studies of new curcuminoid derivatives: Synthesis and characterization. 7th ed. Bioorganic & Medicinal Chemistry Letters. 2016;26:1655-1659.
54. Ding L, Ma S, Lou H, Sun L,Ji M. Synthesis and biological evaluation of curcumin derivatives with water-soluble groups as potential antitumor agents: An *in vitro* investigation using tumor cell lines12th ed. Molecules. 2015;20:21501-21514.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/75758