Review

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Future Medicinal Chemistry

An overview of structure–activity relationship studies of curcumin analogs as antioxidant and anti-inflammatory agents

Curcumin, extracted mainly from *Curcuma longa* rhizomes, has been reported to possess potent anti-inflammatory and anti-oxidant activities. Although safe at higher doses and exhibiting multiple biological activities, curcumin still has the problem of poor bioavailability which has been an attractive area of research over the last few years. A number of efforts have been made by modifying structural features of curcumin. This review highlights the structurally modified and more stable newly synthesized curcumin analogs that have been screened against antioxidant and anti-inflammatory activities. Also the structure–activity relationship to gain insight into future guidelines for scheming new compounds has been discussed, and further these analogs being more stable may serve as promising agents for use in different pathological conditions.

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Inflammation being a central element of innate immunity and inflammatory response emerged in higher animals workout as a protective mechanism, to defend them against injury and infection. The acute inflammatory response is usually self-limiting, resulting in tissue remodeling and normal tissue homeostasis. However, if the system fails to return to normal homeostasis or there is unabating inflammation, it results in chronic inflammation, identified as a root cause in the development of a variety of diseases [1]. The membrane phospholipids produce a 20-carbon unsaturated fatty acid, arachidonic acid (AA) and its derivatives are considered as important mediators of inflammation. The release of AA from membrane phospholipids in response to certain stimuli is mediated through enzyme PLA_2. After releasing, AA is first converted into PGG_2 and PG H_2 in a successive manner with the help of COX-1 or COX-2. Finally, one of the three forms of the enzyme PG synthase causes the catalysis of intermediate PG GH_2 to form the bioactive lipid PGE_2. PGE_2 plays a pivotal role in inflammation by causing vasodilation, increasing vascular permeability, cytokine release and leukocyte migration. Hence, the accumulation of excessive PGE_2 in the body could lead to various diseases such as cancer and cardiovascular diseases [2].

A number of recent researches not only enlightened the significance of AA metabolism in inflammation and associated pathological conditions but also highlighted the modulation of this pathway in the management of numerous diseases. The pro-inflammatory cytokines, IL-6 and TNF-α are also involved in the pathogenesis of numerous inflammatory disorders including rheumatoid arthritis, osteoarthritis, psoriasis and inflammatory bowel disease. Therefore, important targets for the design of novel and safe anti-inflammatory agents include

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the inhibition of enzymes involved in AA pathway as secretory PLA_2 ($sPLA_2$), COX and LOX as well as pro-inflammatory cytokines [3].

Oxygen has an invaluable importance for all the living organisms, as it is required by the cells for the production of energy in the form of ATP. Although it is imperative but sometimes it becomes lethal reflecting oxidative stress [4]. Oxidative stress is referred to a condition when the body's defense system is insufficient to neutralize excessive ROS and their resulting damage [5]. The mitochondria reduce about 2% oxygen, which is converted into free radicals and peroxides. Superoxide and peroxide then interact with metals through oxidation–reduction reactions causing an increased production of radicals particularly hydroxyl radicals. These reactive species are destroyed by normal defense mechanism when generated at low levels. However, when produced at higher levels, they react with different components of the cell, for example, lipid membrane, proteins and DNA ultimately, leading toward the pathogenesis of certain diseases. Moreover, peroxidation of membrane lipids and oxidative destruction of DNA and proteins are believed to be associated with a variety of chronic pathological complications such as cancer, atherosclerosis, diabetes, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease and so forth [6,7].

Turmeric has a wide range of biological activities and has been used for a number of diseases over many decades. Curcumin, the active constituent of turmeric, is a hydrophobic polyphenol isolated mainly from the rhizomes of *Curcuma longa* [8]. It also exhibited a broad spectrum of activities including antibacterial, anti-inflammatory, antiseptic, antioxidant, antimalarial, insect repellant, hypolipidemic, hepatoprotective, wound-healing in addition to protease inhibitor and lipid peroxidase inhibitor effects [9–17]. Curcumin has also been found to modulate several different transcription factors, cytokines, growth factors, kinases along with the inhibition of angiogenesis, proliferation of cancer cells, chemo preventive activities and cytotoxic potential against tumor cells [18–30].

Curcumin as an anti-inflammatory & antioxidant agent

The modern medicine field is confronting the challenge of searching a highly safe and potent anti-inflammatory agent as diverse array of diseases are caused by irregular process of inflammation. Most of the desired remedial effects of curcumin have also been linked with its antioxidant and anti-inflammatory properties [31]. Numerous studies are evident that curcumin is a potent anti-inflammatory agent and it exerts anti-inflammatory effect through a number of mechanisms [32–34]. First, curcumin causes the inhibition of transcription factor NF-κB and AP1, responsible for regulating the expression of pro-inflammatory genes [35–39]. Second, it ceases the activity of COX-2, an enzyme supposed to be involved in many types of inflammation [40–42]. Meanwhile, curcumin by binding to the active site of another enzyme, 5-LOX, involved in LOX pathway, inhibits its activity [43,44]. In addition, curcumin downregulates the expression of various pro-inflammatory and inflammatory cytokines including TNF, IL-1, IL-6, IL-8 and chemokines [22,45,46]. Above all, curcumin is a potent antioxidant, contributing toward its anti-inflammatory action [47–50]. These studies confirmed the anti-inflammatory action of curcumin, established for thousands of years. Owing to its anti-inflammatory activity curcumin has been shown to be efficacious against numerous inflammatory diseases, including pancreatitis, arthritis, inflammatory bowel disease, colitis, gastritis, allergy, autoimmune diseases and cardiovascular problems [51–61]. As in diabetes mellitus, by inhibiting the NF-κB activation and suppression of TNF expression, curcumin stimulates the resistance to insulin [62]. Likewise, curcumin anticipates the cardiovascular problems by inhibiting platelet aggregation, fibrinogen synthesis and inflammatory processes [29,63]. For neurodegenerative diseases such as Alzheimer's disease, curcumin inhibits the inflammation induced by amyloid [64].

Antioxidants are deemed to impede or arrest the disease and nowadays antioxidants are considered as appealing strategy for treating various problems. Numerous lines of evidence suggest that curcumin exhibits its antioxidant potential by repressing lipid peroxidation, raising intracellular level of glutathione along with its binding ability to iron [48,65,66]. The structure of curcumin (**1**) (Figure 1) also corresponds to a unique antioxidant, having a variety of functional groups, holding the β-diketo group, carbon–carbon double bonds and phenyl rings with varying amounts of hydroxyl and methoxy substituents [31]. A number of studies reported that the antioxidant activity of difurolyl methane is due to either phenolic group or the central methylenic hydrogen thus, there are conflicting reports concerning the structural activity of antioxidant activity of curcumin (Figures 2 & 3).

Curcumin, in spite of targeting multiple pathways in biological system, still has been documented to be a safe drug even at higher doses (12 g/day) [67]. The main concern which made this multitargeting agent an attractive area of research is its poor bioavailability at both plasma and tissue levels. Poor absorption, over active metabolism and rapid excretion from the body are among the major reasons limiting the therapeutic use of curcumin. Upon oral administration, curcumin

causes the formation of glucoronides and sulphates, as a result of hepatic conjugation and has been shown to undergo reduction, on systematic administration. To improve the cellular uptake and bioavailability of curcumin, numerous strategies have been undertaken. These efforts include adding curcumin with adjuvant such as piperine in a formulation; use of novel drug delivery system such as curcumin nanoparticles and liposomes; complex formation of curcumin and modification of structural features of curcumin. Among all, the strategy of structural modification has been reported to reach a limited success culminating in analogs with better stability and rapid absorption. Basically, the structure of curcumin belongs to the linear diarylheptanoid class with two oxysubstituted aryl moieties that are linked through a heptadiene linker. The linker is composed of carbonyl groups, enone and oxo functional moieties along with unsaturation in the chain [68] (Figure 1). The β-diketone moiety is assumed to be metabolized by liver enzymes (aldo-keto reductase), reducing the beneficial effects of this phytochemical on different diseases. Therefore, designing the analog by eliminating the unstable β-diketone moiety with the presence of phenolic groups renders the increased bioavailability of curcumin [69].

Generally, curcumin analogs are classified in three groups: analogs from turmeric, analogs from Mother Nature and synthetic analogs. Curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) collectively called curcuminoids, are three analogs from turmeric differing in methoxy substitution on the aromatic ring. Analogs from the Mother Nature are bioactive compounds that occur naturally having some structural similarity to the curcumin molecule, or at least containing one aryl function with 3/4 substitution. Both of these aforementioned analogs have a number of established biological activities. Synthesis of new curcumin-like compounds by modification of basic structure using different chemical reactions is further classified into three groups. These are 'curcumin derivatives', 'curcumin analogs' and 'metal complexes of curcumin'. Compounds that retain the basic structural features of curcumin, such as the seven carbon linker, and the oxy substituents on the benzene rings, are designated as curcumin derivatives while all other compounds with some apparent structural analogy to curcumin are called curcumin analogs. The third group contains the compounds in which curcumin is complexed with some metals [8]. Scientists have used different laboratory methods involving multiple types of catalysts for the synthesis of curcumin analogs. The most common method was found to be a Claisen-Schmidt condensation reaction, between a ketone and aldehyde in the presence of a polar solvent.

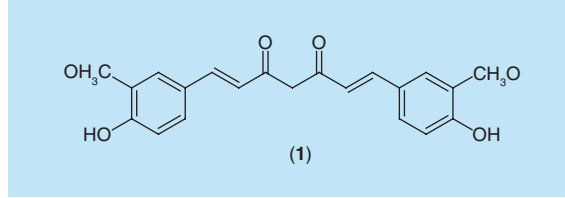


Figure 1. Structure of curcumin.

Various curcumin analogs have been synthesized and evaluated for activity against multiple biological targets. This review highlights the structurally modified and more stable newly synthesized curcumin analogs that have been screened against antioxidant and anti-inflammatory activities. Also the structure–activity relationship (SAR) to gain insight into future guidelines for scheming new compounds has been discussed.

Antioxidant properties of curcumin analogs

Youssef *et al.* reported a new series of curcumin analogs for their *in vitro* antioxidant activity against diphenylpicrylhydrazyl (DPPH) free radical test [70]. The free radical scavenging activity was also measured by chemiluminescence using polymorphonuclear leukocytes (PMNs). The results revealed that six compounds at 100 μg/ml exhibited high% inhibition of free radicals with values greater than 90%, while compound **2** showed the highest% inhibition. In addition, the tested analogs demonstrated that p-hydroxy phenolic structure and electron-donating substituents on the ortho position of benzene ring are some structural requirements for enhanced antioxidative activity. While the removal of active methylene group from the structure resulted a decrease in the antioxidative activities [70].

In another study, a new set of curcumin analogs were synthesized and their antioxidative activity was evaluated through lipid peroxidation assay. Most of the analogs (1.2 μmol) were found to be active against AAPH- and Cu^{2+}-induced low-density lipoprotein (LDL) peroxidation [71]. While other compounds showed weak inhibition and considered almost inactive. The authors identified compounds **3** and **4** as the most potent one and explained that the presence of ortho-diphenoxyl functionality results in remarkably higher antioxidant activity than curcumin and other analogs, and also 4-hydroxyl-3-methoxyphenyl group acts as an important part in the antioxidative activity. The diminished antioxidant activity of the compounds may be attributed to the absence of phenolic group. This is in accordance to Youssef *et al.* who indicated that the phenolic substituent was essential for antioxidant activity [70].

In another study, new 14 3,4-dihydropyrimidine analogs of curcumin were synthesized and assessed for antioxidant activity. The compounds were exam-

ined at a concentration of 50 µmol against DPPH scavenging assay. The reported results indicated that four compounds (**5a, 5b**, **5c** and **5d**) displayed strong DPPH inhibitory activity with percentage inhibition of 88.9, 90.9, 89.5 and 86.3%, respectively. The structural components in relation to activity revealed and strengthened the aforesaid studies that phenolic hydroxyl group is responsible for antioxidant activity [72].

Similarly, another study reported synthesis and antioxidant effects of curcumin pyrazole, N-(substituted) phenyl pyrazole derivatives of curcumin and Knoevenagel condensates of curcumin. The antioxidant activity was determined by using DPPH scavenging assay and it was recorded that pyrazole curcumin exhibited enhanced scavenging effects in comparison to other derivatives which was attributed due to the removal of keto–enol tautomerism as well as central methy-

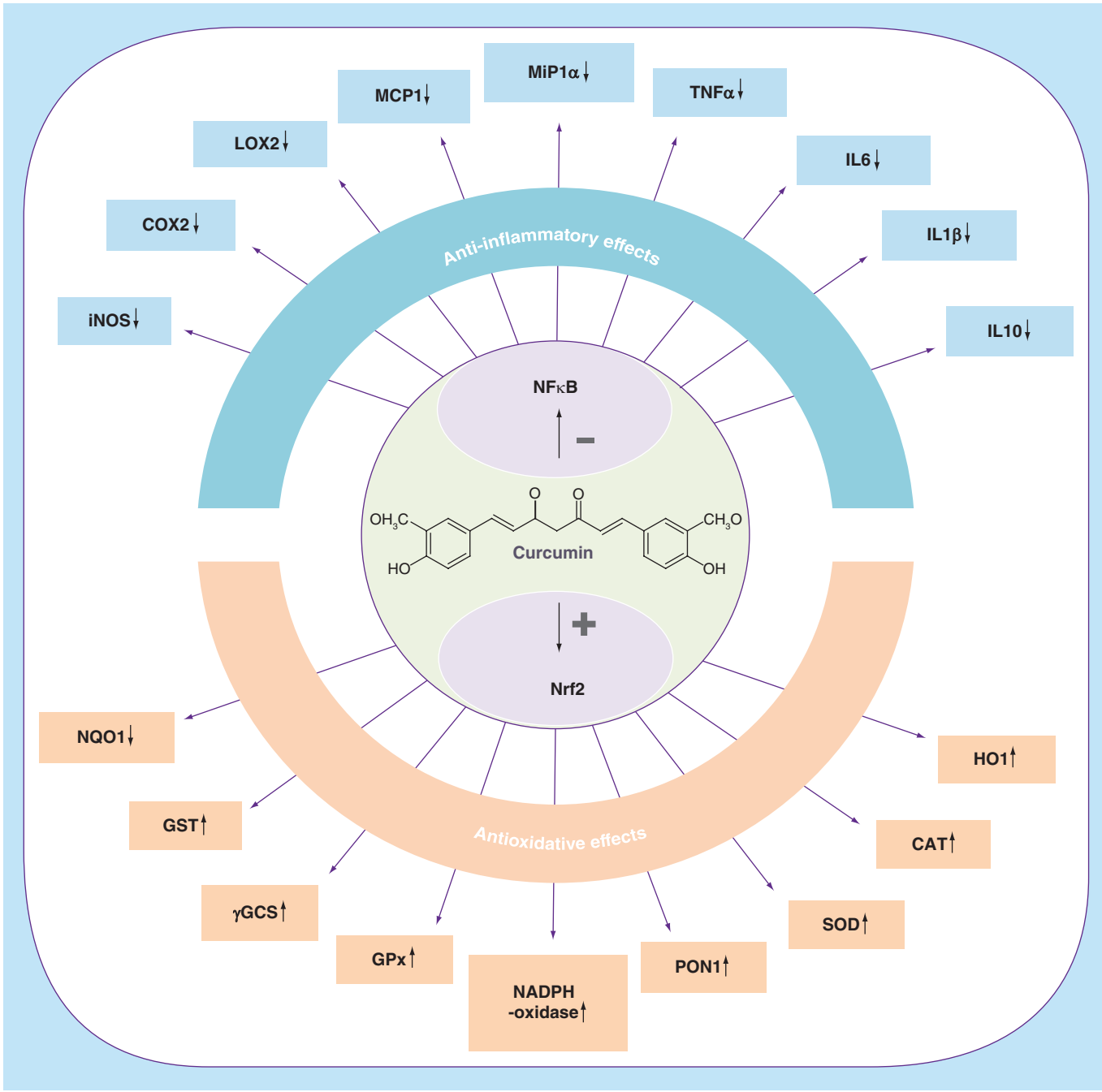


Figure 2. Anti-inflammatory and antioxidative properties of curcumin through the NF-κB and Nrf2 signaling pathways.
iNOS: Inducible nitric oxide synthase; LOX-2: Lipoxygenase-2.

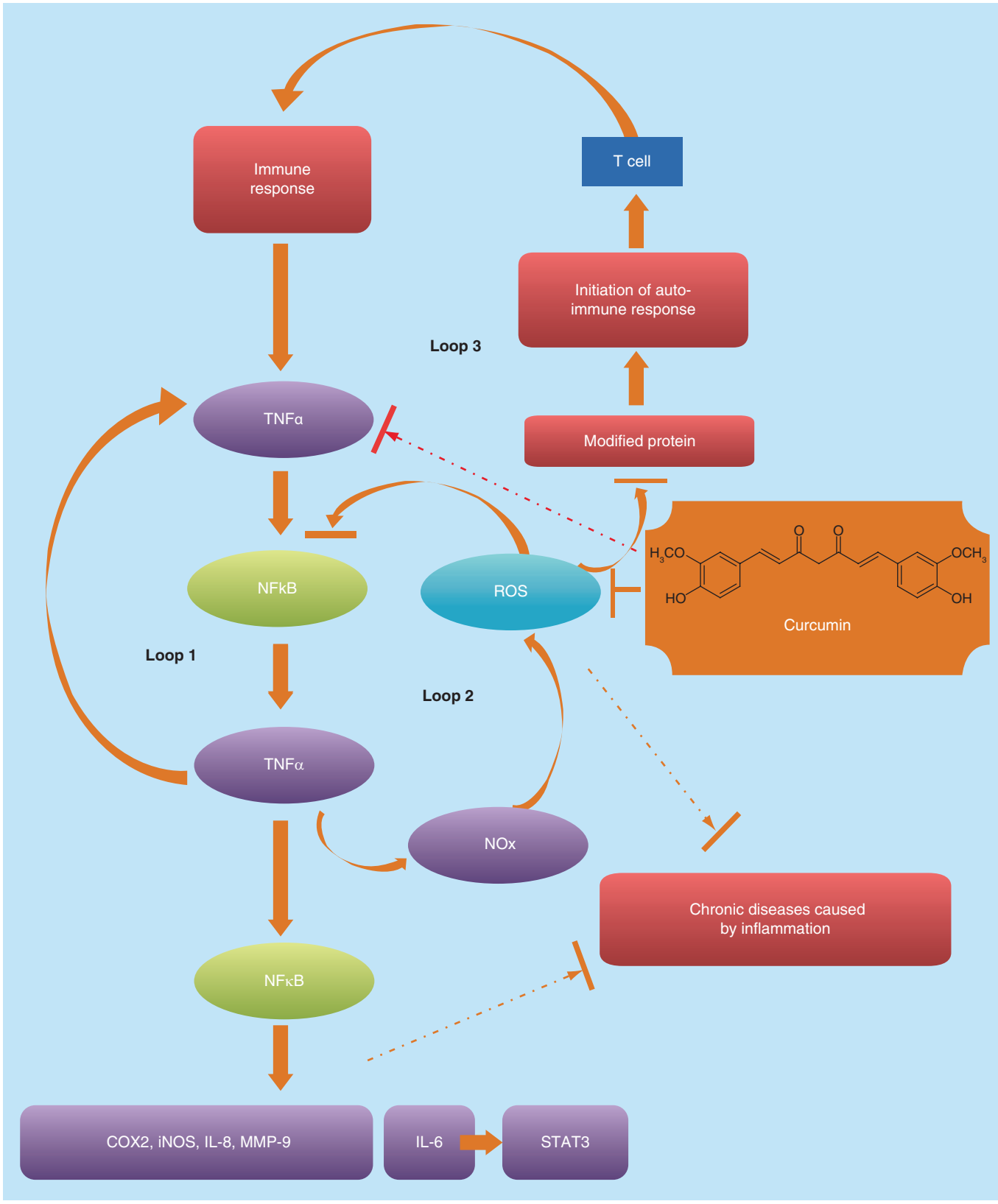


Figure 3. Relationship among reactive oxygen species, chronic inflammatory disorders and antioxidative activities of curcumin.
COX2: Cyclooxygenase-2; iNOS: Inducible nitric oxide synthase.

lene group of heptadiene link in addition to hydroxyl group [73].

Weber *et al.* reported newly synthesized enone analogs including: curcumin analogs with the 7-carbon spacer, 5-carbon spacer and 3-carbon spacer between the aryl rings [74]. Some of the members in these series preserved the phenolic ring while others were deficient of aforesaid group. Telomeric repeat amplification protocol and the ferric reducing antioxidant power (FRAP) assays were used to confirm the anti-oxidant activities of these analogs at a concentration of 10 μmol. The work revealed that compounds possessing phenolic group illustrated the anti-oxidant activity comparable to curcumin. The authors reported another observation in their study that the analogs lacking phenolic substituents were also found active which is in contrast to the previous work in which the presence of phenolic group was considered essential for antioxidant activity. The activity of compounds without phenolic groups was due to formation of stable carbon-centered radicals but still the mechanisms for antioxidant activity of such analogs need to be determined [74].

DPPH scavenging assay was used to evaluate the antioxidant potential of a novel series of enone analogs of curcumin. The results of the study revealed that four compounds exhibited higher scavenging activity as compared with ascorbic acid and curcumin, while compound **4** was found to be highly potent antioxidant agent with an IC_{50} value of 6.73 μmol. SAR analysis revealed that o-diphenoxyl and o-dimethoxyphenoxyl groups are responsible for increased antioxidant activity. Furthermore, the authors suggested that the introduction of ring in the series caused a decline while the electron donating groups at the ortho position resulted in enhanced scavenging potential [75].

In a study conducted by Selvam *et al.*, DPPH radical scavenging assay was employed to estimate the *in vitro* antioxidant potential of newly synthesized pyrazole and isoxazole analogs of curcumin [76]. All the compounds bearing methoxy phenolic compounds demonstrated significant antioxidant effect comparable to curcumin. However, three compounds possessing two methoxy groups showed higher antioxidant activity than the reference compound, trolox and the other curcumin analogs, justifying that the ortho-methoxy substitution improved the stability of the phenoxy radical. Among these three compounds, compound **6** at 100 μg/ml demonstrated better scavenging activity than the other two compounds which may be linked to the presence of pyrazole NH [76].

In search of a more potent antioxidant agent, Al-Omar *et al.* introduced a new series of pyrano[3,2-c] pyridines, pyrazolo[4,3-c]pyridines and pyrido[4,3-d] pyrimidines that were synthesized using some of the α,β-unsaturated cyclic ketones [77]. The antioxidant potential of the compounds on isolated PMNs from the blood of healthy donors was evaluated against free radical scavenging activity *in vitro*. Most of the compounds at a dose of 100 μg/ml showed excellent ability to scavenge oxygen free radicals with percentage inhibitions of greater than 99%, which was comparable to the curcumin potency. The highest inhibition was shown by analog **7** (99.8%), and in perspective of SAR, the introduction of OCH_3 at the ortho-position yielded compounds with higher activity corresponding to the previous study conducted by Selvam *et al.* [76]. The enhanced free radical scavenging activity may be due to stabilization of the phenoxy-free radical as an effect of OCH_3. In addition, elongation of the alkyl chain on the piperidine-N, seemed to be contributing toward the inhibitory effect. And the fused rings pyrano[3,2-c]pyridine, and pyrido[4,3-d]-pyrimidine retained the antioxidant property while the pyrazolo[4,3-c] pyridine series proved to be of diminished activity [77].

Recently, Bukhari *et al.* assessed the inhibitory abilities of 17 diarylpentanoid analogs of curcumin against the reactive ROS production [78]. The chemiluminescence assay was performed by using human whole blood and isolated PMNs. It was reported that compounds **8a** and **8b** at 12.5 μg/ml showed strong inhibition on intracellular and extracellular ROS production with IC_{50} values ranging from 4.2 to 6.2 μmol. Therefore, the study showed that 2-methyl-4 aniline substituent was needed to arrest intracellular and extracellular ROS production [78].

A series of novel curcumin analogs were synthesized by Claisen-Schmidt condensation of various aromatic and heteroaromatic amides of 3-aminoactophenones with 3-bromo-2,4,6-trimethoxybenzaldehyde and were evaluated for anti-oxidant activity. *In vitro* assays like DPPH and OH radical scavenging assay along with the reducing activity assay were used. In comparison to standard gallic acid (92.30% inhibition), the compounds (1 mM) showed mild antioxidant activity with percentage inhibitions ranging from 44.30 to 49.44%. Compound **9** (54.14% inhibition) with aromatic amide and hetero aromatic nucleus showed potent hydroxyl radical scavenging ability as compared with ascorbic acid (45.85% inhibition) and the presence of these two structural moieties was considered to be responsible for the antioxidant potential [79].

Recently, newly synthesized 2-benzoyl-6-benzylidene-cyclohexanone analogs were investigated for their antioxidant activity through DPPH, FRAP and NO scavenging assays. The results analysis revealed that two compounds were found to display significant activity in both DPPH and FRAP assays and compound **10** (200 μmol) demonstrated a remarkably high antioxi-

dant potential. In DPPH analysis, the activity seemed to be double than curcumin while it was equipotent to butylated hydroxytoluene in FRAP scavenging assay. On the contrary, all the tested analogs remained inactive during the direct NO scavenging activity. Detailed relationship with the structure was not determined however it was concluded that 3,4-dihydroxylphenyl ring was a central moiety for biological activities of the 2-benzoyl-6-benzylidenecyclohexanone analogs [80].

In another study, the *in vitro* antioxidant effects of a newly developed curcumin analog were explored using three different scavenging assays namely DPPH, lipid peroxidation and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) cation radical scavenging assay. The author labeled the new analog as A_2. The observations from the data lead to the conclusion that antioxidant activity of A_2 increased twofold in comparison to curcumin with 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) assay while it was four-times stronger in DPPH assay. The unusual results were seen in lipid peroxidation assay where this analog of curcumin displayed 24-fold enhanced antioxidant activity demonstrating that it may serve as a promising antioxidant agent. However, structural components responsible for such a remarkably high antioxidant potential were not explained in the study [66].

Lately, several new analogs of curcumin have been prepared and their antioxidant potential was investigated against rat pheochromocytoma (PC-12) cell model and it was reported that all compounds exhibited modest hydroxyl radical scavenging activity, but compounds **11a** and **11b** showed good antioxidant activity with EC_{50} values of 25.6 and 31.4 μmol, respectively. However, SAR studies were not discussed regarding the activity of this novel curcumin analog [81]. Table 1 refers to the various antioxidative activities of curcumin analogs and Figure 4 shows the chemical structures with potent antioxidant activity.

Anti-inflammatory properties of curcumin analogs

Regulation of COX & LOX pathways by curcumin analogs

The nonimmune mechanism of anti-inflammatory properties of curcumin has been applied through suppression of PGs synthesis [82]. The principle enzyme responsible for the conversion of AA to PGs is cyclooxygenase. It consists of two different isoforms, designated COX-1 and COX-2. COX-1 is a constitutive isoform present in most tissues maintaining the normal physiological processes and mostly viewed as a 'housekeeping' enzyme [83]. In contrast, COX-2 is constitutively expressed only in brain and spinal cord tissue; however, this form can be induced. Various stimuli such as mitogens, oncogenes, tumor promoters, growth factors and the inflammation process itself serve as stimuli for COX-2 expression [84]. COX-2 over expression has been connected to the carcinogenesis of various tumors for example neck, lung, pancreas, stomach colon, rectum and breast [85]. There is also growing evidence that inhibitors of COX-2 activity are effective for treating inflammation and preventing or treating cancer [86]. However, some studies suggested that COX-1 and COX-2 dual inhibitors were more appropriate for treating chronic inflammation [87]. In addition to COX pathway, LOX pathway is considered to play an important role in the process of inflammation and associated diseases. AA is cleaved from membrane phospholipids, upon receiving signal neutrophil's activation, and can be converted into leukotrienes through LOX enzyme. LTB4 is a potent mediator of inflammation, enhancing recruitment and activation of inflammatory cells hence leading toward the pathogenesis of various inflammatory diseases [88].

A number of studies documented that COX-1 is constitutive while COX-2 being inducible is expressed only during inflammation. Compounds that selectively inhibit COX-2 are considered to be better anti-inflammatory agents. Selvam *et al.* have provided the evidence when they studied newly synthesized pyrazole and isoxazole analogs for their anti-inflammatory activity [76]. The designed analogs were investigated against COX-1/COX-2 inhibition using both *in vitro* and *in vivo* assays. *In vitro* (PG biosynthesis assay) experiment revealed that some compounds (100 μmol) demonstrated good COX inhibitory activity while other analogs seemed to be better COX-2 inhibitors in comparison with curcumin. The selected compounds were further investigated for *in vivo* anti-inflammatory activity using carrageenan-induced rat paw edema (CPE) assay. Among these compounds, curcumin analog **4** (75 mg/kg) was found to have the highest% inhibition and enhanced selectivity toward COX-2. The authors concluded that substitution of β-diketone moiety of curcumin by a pyrazole ring increased COX-2/COX-1 selectivity to many folds and hence increased the anti-inflammatory activity [76]. Curcumin analogs with potential inhibitory effects on COX-1 and COX-2 are shown in Figure 5.

Lee *et al.* described four diarylheptanoid analogs and a series of new diarylheptylamine analogs as COX-2 inhibitors [89]. These compounds were structurally related to natural anti-inflammatory agent, oregonin and prepared by the modification of curcumin. The anti-inflammatory activity of the prepared compounds was evaluated by using lipopolysaccharide (LPS) stimulated macrophages for induction of COX-2 as a model system. The results demonstrated

Table 1. Antioxidant properties of curcumin analogs.

Functional group promoting activity	Ref.
Phenolic group at para position electron donating substituent at ortho position of benzene ring	[70]
Ortho diphenoxyl functionality 4 hydroxyl, 3 methyl phenyl group	[71]
Phenolic hydroxyl group	[72]
Central methylene group of heptadiene link and hydroxyl group	[73]
Presence of phenolic group and carbon-centered radicals	[74]
Ortho-diphenoxyl and ortho-dimethoxy phenoxyl group	[75]
Presence of pyrazole NH	[76]
OCH3 group at ortho position	[77]
2-methyl-4-aniline substituent	[78]
Aromatic amide and hetero aromatic nucleus	[79]
3–4 dihydroxylphenyl ring	[80]

that diarylheptylamine and diarylheptanoid analogs could inhibit COX-2 responses of LPS, although, less potently than oregonin. However, these compounds strongly inhibited COX-2-catalyzed PGE_2 biosynthesis as compared with oregonin. Among these, hexahydrocurcumin (**12**) was the most potent with an IC_{50} value of 0.7 µmol. The structural features relating to the anti-inflammatory effect was not explained by the author in the study [89].

Contrary to previous studies, Handler *et al.* examined a series of newly synthesized curcumin analogs as highly selective COX-1 inhibitors as some studies reported that COX-1 is involved in various carcinoma and inflammatory diseases [90]. These compounds were assessed against COX inhibition using a COX inhibitor screening kit. All curcumin analogs showed a high rate of COX-1 inhibition but compound **13** was found to be the most potent curcumin analog. It was observed that lipophilic and polar substituents on the phenyl ring, like methoxy or methyl ester groups improved the specificity of the compounds [91].

Bandgar *et al.* evaluated the anti-inflammatory activity of a series of novel curcumin analogs and found that they were selective COX-2 inhibitors [79]. This series containing enone and amide with trimethoxy benzene moiety were synthesized by Claisen-Schmidt condensation. The synthesized compounds were subjected to colorimetric COX inhibitor screening assay. The percentage inhibition values (89.25–83.28%) showed that the compounds exhibited potent and preferential COX-2 inhibition with compound **14** exhibiting the highest activity. The structural components found to be responsible for cyclooxygenase inhibition were those containing electron-withdrawing substituents on amide ring. Also it was reported that substituent position plays a pivotal role in determining the activity and change of fluorine from para to meta and from meta to ortho resulted a further decrease in activity [79].

Recently a series of unsymmetrical monocarbonyl curcumin analogs were synthesized by Aluwi *et al.* in an effort to support the findings of previous studies that unsymmetrical form might possess greater biological activity as compared with symmetrical one [2]. They used human and murine macrophages stimulated by LPS to determine the *in vitro* inhibitory effects on PGE_2 production. Compound **15** at 25 µmol with dimethoxyl group and furanyl ring exhibited strong inhibition on the secretion of PGE_2 in RAW 264.7 and U937 cells. Molecular docking studies confirmed that the anti-inflammatory activity of the compounds was due to inhibition of COX-2 enzyme. To improve the potency, vanillin was placed at position Ar_2 and it was observed that compounds **16a** and **16b** with IC_{50} values of 0.78 and 1.9 µmol, respectively, significantly lower the PGE_2 secretion level. Hence, it was concluded that the addition of vanillin moiety was sufficient to double the activity of curcumin and the presence of furanyl ring in compounds significantly enhanced the PGE_2 inhibition in both macrophages cells [2].

Yuniarti *et al.* described *in vitro* and *in silico* studies of some analogs of curcumin as dual inhibitors of COX-1 and COX-2 with the view that, such compounds were suggested to be more appropriate for treating chronic inflammation in comparison to selective inhibitors [87]. The compounds used were 2,5-bis(4-hydroxyl-3-methoxybenzilidene)-cyclopentanone and 1,5-bis(4-hydroxyl-3-methoxyphenyl)penta-1,4-dien-3-one and compared with curcumin. Colorimetric COX inhibitor screening assay was used to determine the inhibitory activity. The authors reported that all the designed analogs (15 µmol) were found to be potent inhibitors toward both COX-1 and COX-2. Although, minor selectivity trend for each compound was observed but statistical

data revealed that the differences were trivial at 95% level of CIs. SAR was not determined in the study [87].

Bukhari *et al.* reported anti-inflammatory activity of newly synthesized α,β-unsaturated carbonyl-based compounds as inhibitors of COX-1 and COX-2 along with LOX enzyme [3]. Six α,β-unsaturated carbonyl-based compounds displayed strong inhibition of $sPLA_2$ activity, but compound **17a** resulted in remarkably high activity. On the other hand, compounds **17b** and **17c** exhibited the highest COX-1 and COX-2 inhibitory activity with COX inhibitor screening kit. In a standard calorimetric assay, compound **17d** exhibited strong inhibition of LOX enzyme. SAR analysis revealed that the linear or cyclic linkers derived from

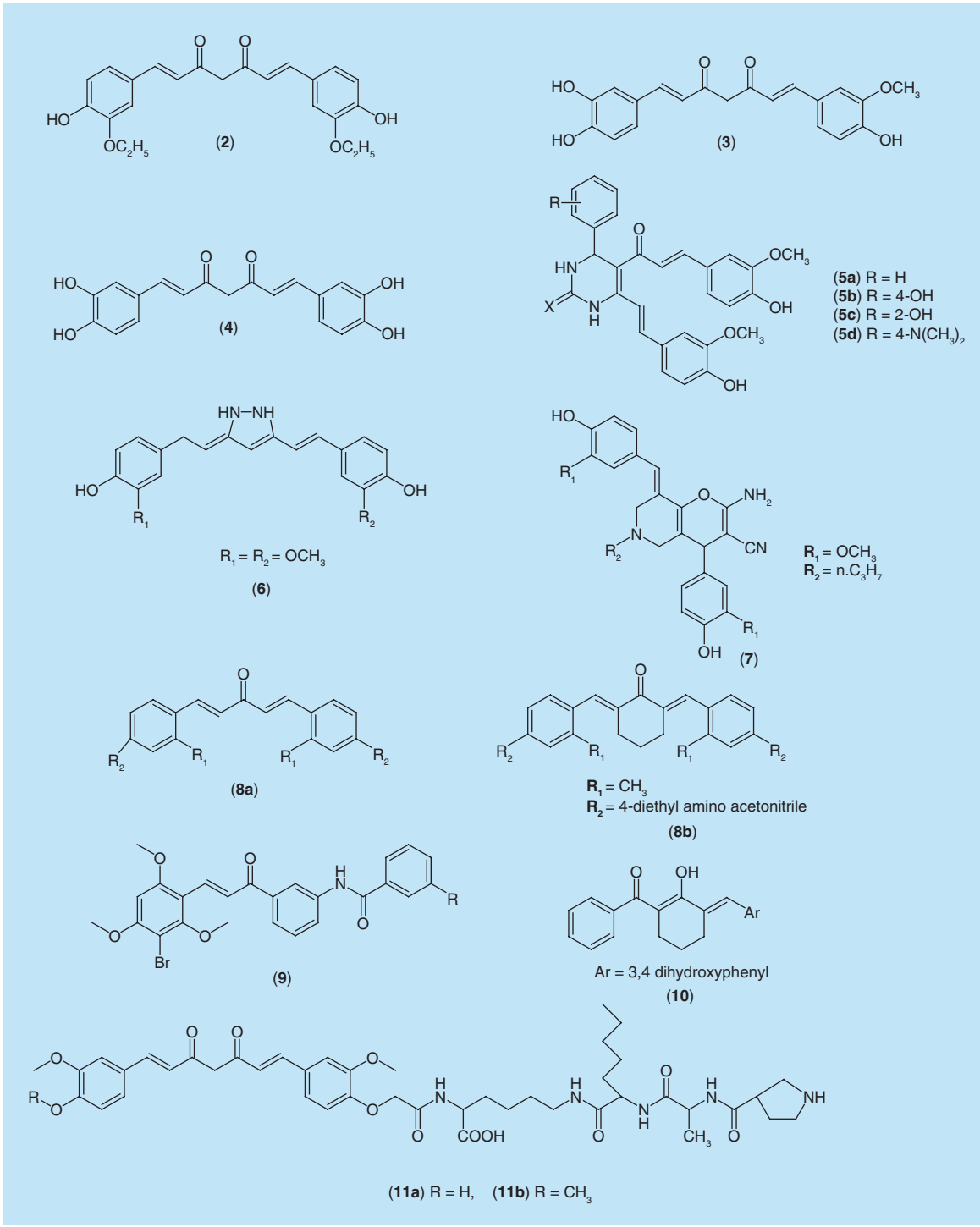


Figure 4. Curcumin analogs exhibiting potent antioxidant activity.

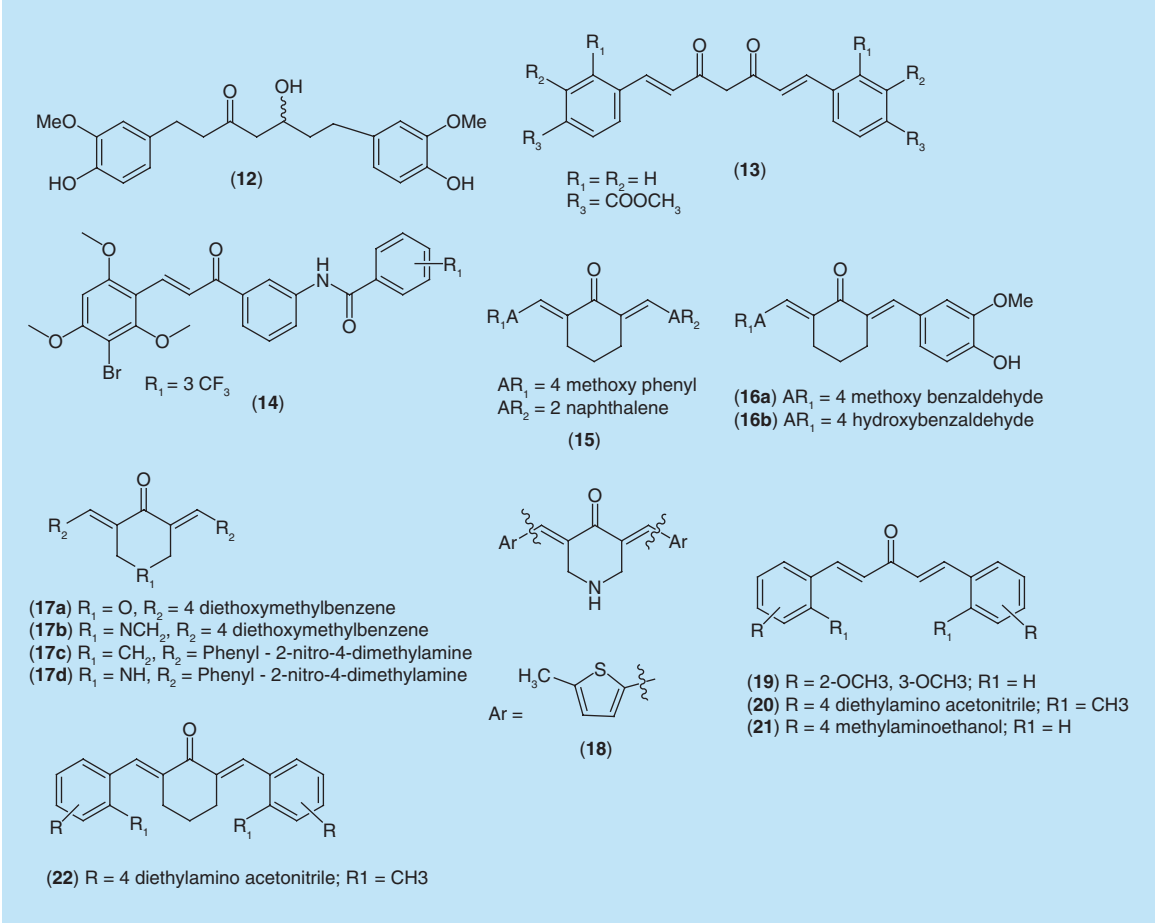


Figure 5. Synthetic curcumin analogs with potent inhibitory effects in COX-1 and COX-2.

ketones between two aromatic rings played an important role in terms of inhibitory activity. In addition, the analogs containing *N*-methyl-4-piperidone linker was found to be strong inhibitor of $sPLA_2$, COX-1 and LOX enzymes while compounds with 4-piperidone linker and tetrahydropyran-4 showed good inhibitory activity but in a decreasing manner as compared with *N*-methyl-4-piperidone linker [3].

Based on the previous studies [92,93], Katsori *et al.* designed a series of novel curcumin analogs with a variety of heterocyclic rings (indolyl, imidazolyl, thienyl) and the naphthyl ring with a view that the presence of heteroaromatic cores was associated with potent anti-inflammatory activities. The compounds were investigated as potential agents to inhibit LOX enzyme in both *in vitro* and *in vivo* models. The *in vitro* study was performed by UV absorbance-based enzyme assay while *in vivo* anti-inflammatory effect was assessed by using the CPE model. The study demonstrated that curcumin analogs bearing heterocyclic substituents in the aromatic part were proved more potent *in vitro* inhibitors of enzymes than curcumin, whereas *in vivo* assay presented compound **18** causing the highest inhibition of CPE, among the tested compounds. The naphthyl analog exhibited marked inhibitory activity in both assays. The influence of lipophilicity was well documented being correlated with the biological activity of the compounds [88].

Ahmad *et al.* synthesized a series of novel diarylpentanoid analogs of curcumin and evaluated their effects on the enzymes of AA metabolism pathway [94]. LOX enzyme activity was examined by a standard calorimetric assay while COX activity was tested through COX inhibitor screening assay kit. On the other hand, a photometric assay was used to determine the PLA_2 inhibition. It was concluded that compounds **19** and **20** at concentrations of 1.25–20 µg/ml showed strong inhibitory effects on the enzyme PLA_2 with IC_{50} values of 10.38 and 5.98 µmol, respectively. Compounds **21** and **22** (40 µg/ml) were found to exhibit highly potent anti-inflammatory activities in COX-1, COX-2 and LOX inhibitory assays. The analysis of SAR showed that compounds bearing 2-methyl-*N*-ethyl-*N*-(2-cyanoethyl)-4-amino exhibited highest inhibition of PLA2 and LOX activities. While diethylamine group at position 4 of both phenyl rings of cyclohexanone and

acetone was found responsible for increased COX-1 activity and diarylpentanoid analogs with *N*-methyl-*N*-(2-hydroxyethyl)-4-amino at the aforesaid position exhibited strong COX-2 inhibitory activity [94].

Effect of curcumin analogs on inducible nitric oxide synthase

Another enzyme that plays a pivotal role in mediating inflammation is inducible iNOS. By catalyzing the oxidative deamination of l-arginine, iNOS yields NO, a potent pro-inflammatory mediator, also involved in the regulation of physiological and pathophysiological mechanisms in cardiovascular, nervous and immunological systems. Abnormal expression of iNOS and excessive NO production may lead to chronic inflammation and also associated with number of diseases such as rheumatoid arthritis, diabetes, hypertension and septic shock. In response to stimuli LPS, iNOS also causes the expression of proinflammatory cytokines including TNF-α, IL-1β and IFN-γ [95].

Initially, Lee *et al.* synthesized diarylheptanoid analogs and a series of new diarylheptylamine compounds by making alteration in the structure of curcumin. For the induction of iNOS, LPS was used to stimulate macrophages and the anti-inflammatory activity of the prepared compounds was tested. The study reported that diarylheptylamine and diarylheptanoid analogs could inhibit iNOS responses of LPS, but less potently than oregonin, a natural anti-inflammatory agent structurally similar to curcumin. However, structure–activity analysis of the compounds was not described [89].

Pae *et al.* examined a more stable synthetic curcumin analog, dimethoxycurcumin (**23**), for NO production [96]. LPS-activated macrophages were used to evaluate the inhibition of NO production and iNOS expression. Dimethoxycurcumin which contains four methoxy groups at two aromatic rings, was compared with curcumin, BDMC containing no methoxy group and tetrahydrocurcumin (THC) containing two methoxy groups but lacking conjugated double bonds in the central seven carbon chain. The results showed that dimethoxycurcumin (DiMC), curcumin and BDMC inhibited NO production, iNOS expression with DiMC being the most effective, followed by curcumin and BDMC. THC did not show any activity. The SAR suggested that the activity might be not only due to the increased number of methoxy groups but also due to the conjugated double bonds. As evident by THC, lacking this functional group was found to be virtually inactive in inhibiting NO production and iNOS expression. Some of the previous studies [97,98], also confirmed that α, β-unsaturated carbonyl group is an important reactive structure of curcumin analogs [96].

Another study, in the following year, reported a newly synthesized series of curcumin related diarylpentanoid analogs to have anti-inflammatory activity. Among the 46 compounds tested, three curcumin-like diarylpentanoid analogs, which are **24a, 24b** and **25** showed remarkably high inhibitory effect upon NO production in RAW macrophages 264.7 as compared with the positive control and curcumin. The presence of 2, 5-dimethoxylated phenyl rings on **24a** and **24b** while 2-hydroxylated phenyl rings on **25** were thought to be contributing toward their potent anti-inflammatory action. Inhibition of target protein was suggested as the mechanism responsible for the anti-inflammatory property of these compounds [99].

In a study conducted by Leong *et al.* a series of 97 diarylpentanoid derivatives with diarylpentenedione series, halogenated, methoxylated and polyphenolic were synthesized [100]. The IFN-γ/LPS-stimulated macrophages cells were used to assess the anti-inflammatory activity through NO suppression assay. Among all the series 12 compounds exhibited greater or comparable NO inhibitory activity with curcumin. However, compound **26** demonstrated the most significant NO suppression activity with an IC_{50} value of 4.9 μmol and also found to exhibit excellent chemical stability. An SAR study revealed the findings in accordance with a previous study that the presence of a hydroxyl group in both aromatic rings was critical for bioactivity of these molecules. Meanwhile, pharmacophore mapping showed that hydroxyl substituents at both meta and para-positions of ring B could be responsible for highly active diarylpentanoid derivatives. The author concluded his study by reporting that the diarylpentanoid structure with preserved ethylene and β-diketone moieties was a primary direction and should be investigated further toward finding new anti-inflammatory agents [100].

In continuation with the previous work, Leong *et al.* reported similar findings in another study [80]. A series of 24 2-benzoyl-6-benzylidenecyclohexanone analogs were evaluated for their *in vitro* NO inhibitory effects. In LPS/IFN-induced RAW 264.7 macrophages model, six compounds (50 μmol) showed significant NO inhibitory activity. Among these six compounds, the highest activity was found to be exhibited by compound **27** with an IC_{50} value of 4.2 μmol. The activity in relation to the structure displayed that phenolic group was imperative for inhibition of NO as evident by five active compounds preserving at least one hydroxyl group in their structures. In the same manner, it has also been found that the desired activity was not affected by the different arrangement of functional groups on the ring. However, the meta-position was recognized as preferable site for substitution of hydrox-

ylated compounds in terms of enhanced NO inhibitory activity [80].

Analogously, Faudzi *et al.* strengthening the results of previous studies evaluated the anti-inflammatory activity of a series of 45 1,5-diphenylpenta-2,4-dien-1-one analogs by measuring their NO inhibition activity [101]. The compounds were synthesized by introducing two rings with different substituents using Claisen-Schmidt condensation method and tested against IFN-γ/LPS-activated RAW 264.7 cells. Among the several compounds, showing similar or greater activity than curcumin, the most significant NO inhibitory activity was manifested by compound **28**, a 5-methylthiophenyl-bearing analog with an IC_{50} value of 10.24 μmol. A detailed study of structural features in biological implication along with 2D and 3D NF-KB analyses were performed. It was concluded that a hydroxyl group on either meta or para position of ring A was an importance feature in the enhancement of NO inhibition activity and an α,β-unsaturated ketone moiety on the linker were crucial for a remarkable anti-inflammatory activity [101].

Contrary to the aforementioned studies, Tham *et al.* introduced a series of curcumin analogs by eliminating the unstable β-diketone moiety and modifying it into conjugated double bonds while preserving the phenolic OH group [102]. The anti-inflammatory and mechanistic effects of compound **29** were studied upon NO inhibition in inflammation models. This synthetic analog showed inhibitory action upon the synthesis of NO in a dose-dependent manner and further it was confirmed that the suppression of iNOS gene and enzyme expression were responsible for the activity rather than an effect upon iNOS synthase activity or nitrite scavenging. Although the structural features investigation was not performed, but it was observed that the removal of ß-diketone moiety from the structure did not affect the activity and showed the NO inhibition [102].

Recently, Bi *et al.* investigated the anti-inflammatory activity of novel curcumin analogs synthesized as hybrid drugs through xylene-induced ear edema model at a dose of 1 μmol/kg. The reported data revealed that compounds **11a** and **11b** demonstrated significant anti-inflammatory potential with percentage inhibition of 62.0 and 57.67%, respectively. These compounds have also been shown to exhibit thrombolytic activities [81]. Chemical structures of all the potent curcumin analogs mentioned above are shown in Figure 6.

Modulation of pro-inflammatory cytokines & transcription factors by curcumin analogs

Pro-inflammatory cytokines such as TNF-α and interleukins particularly IL-6 are critically involved in inflammation and related disorders [103]. The pro inflammatory effects of TNF are primarily due to its ability to activate NF-κB [104]. The most pervasive transcription factors that regulate expression of genes involved in controlling cellular proliferation/growth, inflammatory responses, cell adhesion and so forth NF-κB [105]. Almost all cell types, when exposed to TNF, activate NF-κB, leading to the expression of inflammatory genes. These include COX-2, LOX-2, cell adhesion molecules, inflammatory cytokines, chemokines and iNOS [104]. Therefore, over expressions of TNF-α and IL-6 are responsible for the initiation and extension of pathological disorders including ulcerative colitis, diabetes, multiple sclerosis, atherosclerosis and septic shock. So, anti-inflammatory agents that inhibit the over expression of pro-inflammatory cytokines are of great interest for the clinical treatment of many inflammatory diseases [103].

In one study, Weber *et al.* reported enone analogs of curcumin with 5 carbon spacer (10 μmol) as the potent inhibitors of NF-κB. Enone analogs that retained the 7-carbon spacer between the aromatic rings, a 5-carbon spacer and a 3-carbon spacer were prepared and tested for their abilities to inhibit the TNF-α-induced activation of NF-κB with panomics NF-κB reporter stable cell line 293T/NF-κB-luciferase. Inhibitors of NF-κB activation were identified in all three series. As described earlier, enone analogs in the series with the 5-carbon spacer exhibited the highest inhibitory activity particularly those members that contained heterocyclic rings. Hence, analog **30** was found to be the most active analog, with an IC_{50} value of 3.4 μmol. Further investigation suggested that the role of the enone or dienone functionality in diaryl systems was important but not essential for activity [74].

Pae *et al.* investigated DiMC, a more stable synthetic curcumin analog's ability to inhibit the NF-κB in LPS-activated raw macrophages. The inhibitory activity of DiMC, was compared with BDMC and THC. DiMC, curcumin and BDMC inhibited NF-κB activation with the decreasing order although THC completely failed to inhibit NFαB activation. The results derived from the study leads toward the conclusion that α,β-unsaturated carbonyl group is an important functional group as contained by the three analogs showing the activity but the differential efficiency of the compounds depends on the number of methoxy groups. Further mechanistic elucidation demonstrated that diminished NF-κB activation was by blocking IkBα phosphorylation and IKK-α activity [96].

Liang *et al.* designed three series of monocarbonyl curcumin analogs, 1,5-diaryl-1,4-pentadiene-3-ones, together with cyclopentanone and cyclohexanone analogs, by deleting the methylene group and one carbonyl group and tested *in vitro* anti-inflammatory activity by

using ELISA kits [106]. The results indicated that curcumin and its analogs (10 μmol) inhibited LPS (0.5 μg/ml)-induced TNF-α and IL-6 expression and the cyclohexanone-derived C compounds were more effective than acetone-derived A and cyclopentanone-derived B compounds. SAR studies revealed the role of different substituents on the benzene ring and in the absence of unstable methylene, the influence of five carbon linker on inflammatory activities. The compound **31a**, with (dimethylamino) propoxyl, and compound **31b** with allyloxyl substituent have more potent inhibitory effect than curcumin. However, other compounds with similar substituent showed less inhibitory effects than curcumin, indicating that anti-inflammatory effects were not increased by only nitrogenous substitution [106].

In a sequence with previous study, the author investigated the bioactivity of nine newly synthesized compounds with the same series against LPS-induced TNF-α and IL-6 secretions by using mouse J774.1 macrophages. The results showed that the 3-methoxyl played an important role in bioactivity and cyclohexanone containing analogs exhibited stronger inflammatory inhibition than acetone and cyclopentanone analogs which is in conformity to previous study. Subsequently single-crystal XRD was performed using the most active analog and compared with curcumin. It was concluded that the presence of cyclohexanone in the most active compound **32** may play an important role in the bioactivity [107].

Liang *et al.* evaluated another 44 monocarbonyl analogs with the same series for the inhibitory activities against aforementioned model [108]. Five active compounds were found to inhibit TNF-α and IL-6 release after basic screening. Among these compounds, three were selected to further evaluate the inhibitory effects on several LPS-induced inflammatory mediators such as TNF-α, IL-1, IL-6, MCP-1, COX-2, PGES, iNOS and NF-κB. The results of this study were in accordance with the authors' previous work that monocarbonyl analogs may possess comparable anti-inflammatory activities with curcumin despite the absence of the β diketone functional moiety. However, compound **33** was further investigated by combining with hydrochloric acid against LPS-induced cytokine production. The authors suggested that compound **33** may serve as a promising anti-inflammatory molecule [108].

Likewise, Zhao *et al.* synthesized 23 monocarbonyl analogs of curcumin with a series of 5-carbon linker by removing the unstable β diketone moiety and classified as acetone-derived B-class, cyclopentanone-derived A-class and cyclohexanone-derived C-class. These compounds were reported to have improved pharmaco-

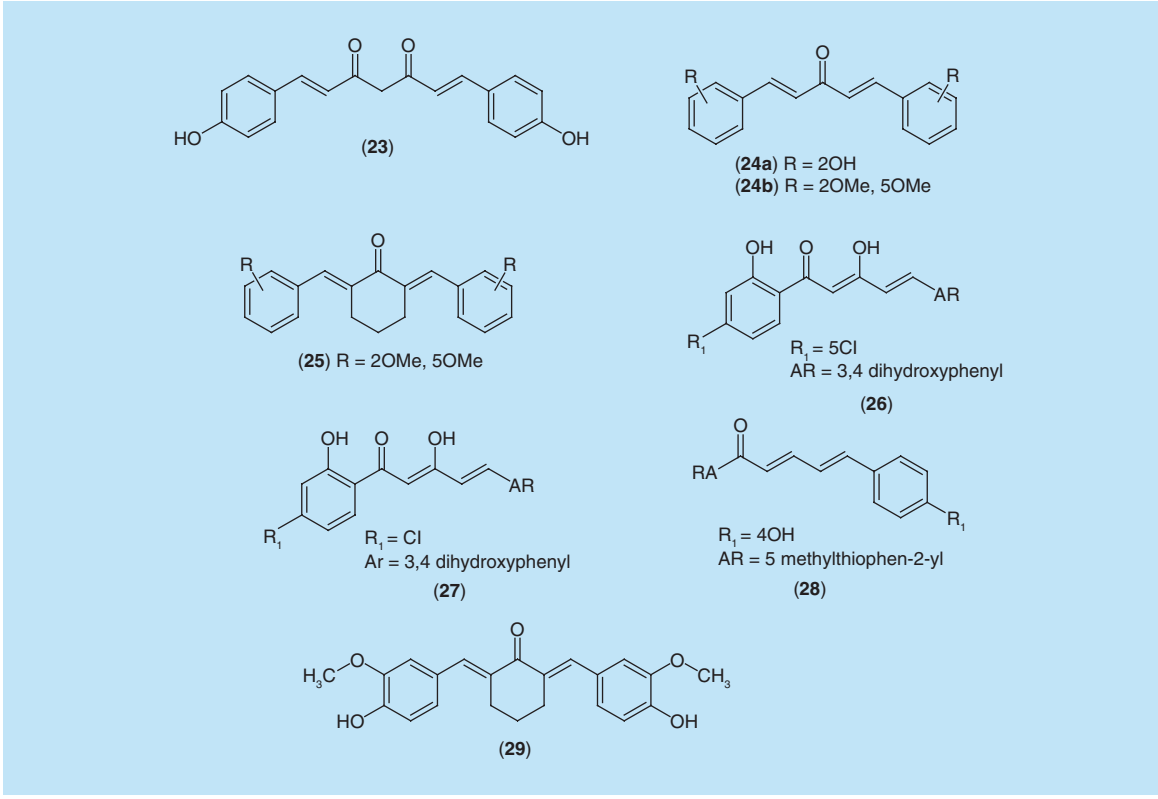
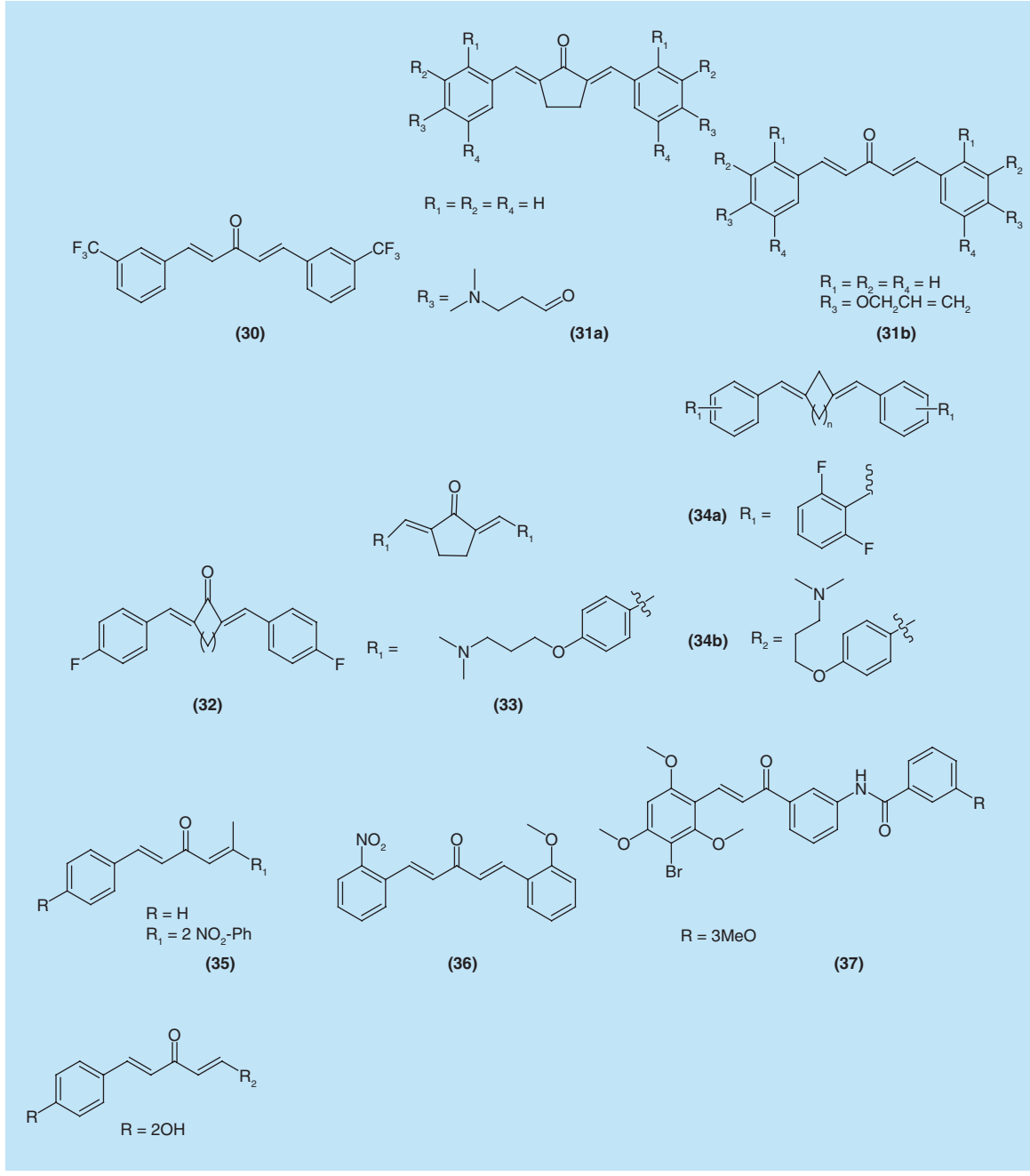


Figure 6. Synthetic curcumin analogs demonstrating potent inhibition of nitric oxide production and inducible nitric oxide synthase.

kinetic profiles both *in vitro* and *in vivo* [92] and were examined for anti-inflammatory activity. The observations recorded were contradictory to the study conducted by Liang *et al.* as acetone-derived B-class analogs were found more effective than cyclopentanone-derived A-class and cyclohexanone- derived C-class, indicating the role of structure, 5-carbon linker on such activities. Compounds **34a** and **34b** were the most potent analogs and showed a dose-dependent anti-inflammatory response in macrophages. With respect to SAR, it was suggested that the electron-donating ability of the 4-substituent might be responsible for enhancing the anti-inflammatory abilities of the monocarbonyl analogs, whereas electric neutrality and electron-withdrawing moiety may reduce bioactivity. Moreover, *N*,*N*-dimethyl-propoxy containing long-chain analogs may be considered as promising compounds for developing anti-inflammatory candidates [109].

Zhao *et al.* studied a novel class of asymmetric monocarbonyl analogs of curcumin. The study involved both *in vitro* and *in vivo* models to determine anti-inflammatory effects. Most of the compounds significantly reduced the production of TNF-α and IL-6 in LPS-stimulated macrophages. SAR analysis revealed that compounds



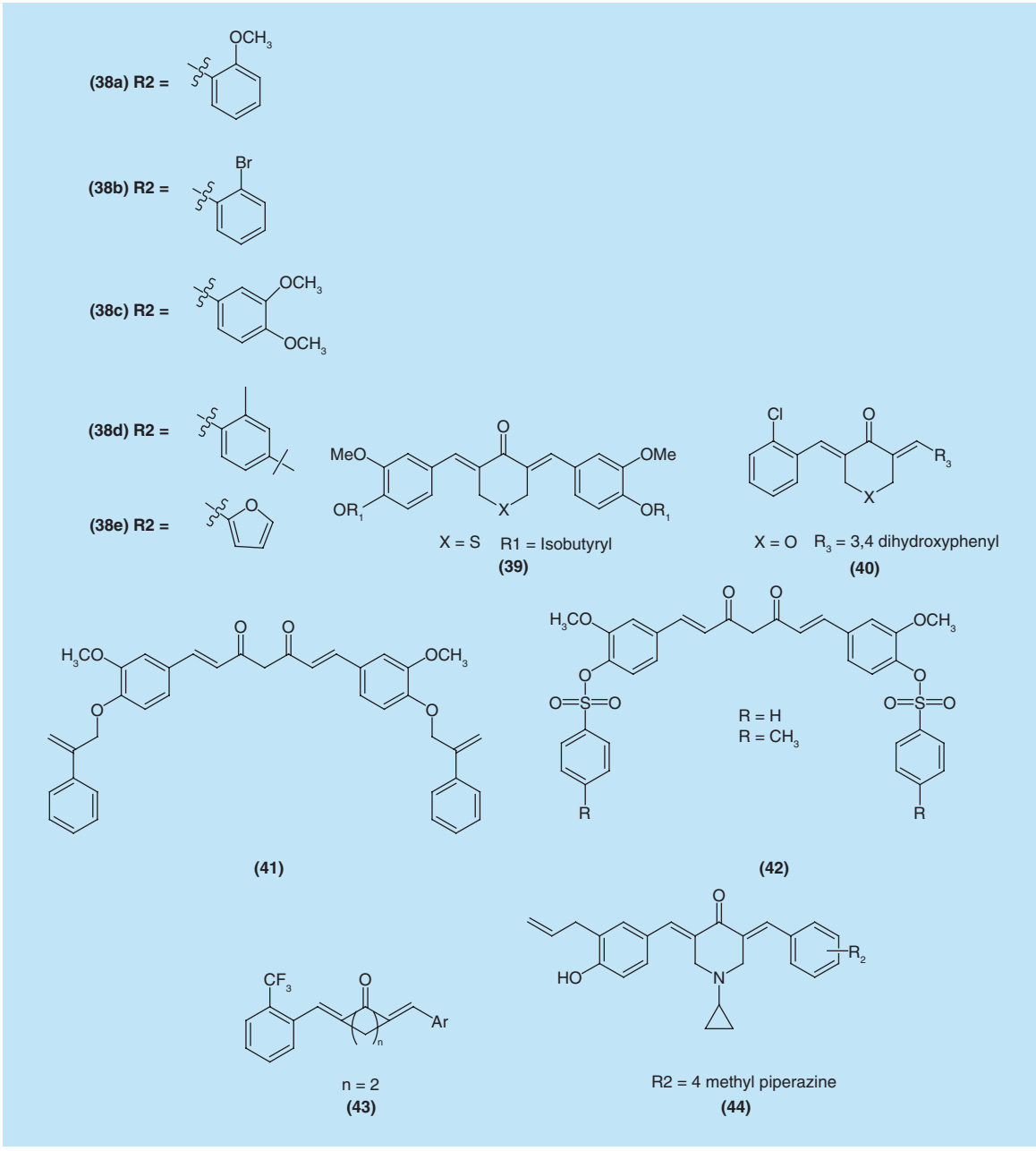


Figure 7. Curcumin analogs with potent inhibitory effects on pro-inflammatory cytokines and transcription factors (cont. from facing page).

with an electron-withdrawing substituent on aromatic ring are likely to exert higher TNF-α inhibition (with the most potent compound **35**, a 2-nitro-substituted compound, having inhibition rate of 91.20%) than those with an electron-donating group. In addition, substitution of benzene ring with thiophene in compounds also increased the inhibitory activity against TNF-α. However, the study lacks relationship of IL-6 inhibition with respect to chemical features. Further investigation into the possible mechanism revealed that the anti-inflammatory activity of the analog might be correlated with its inhibition of NF-κB and ERK pathway activation [103].

Zhang *et al.* obtained results that were in agreement to those reported by Zhao *et al.* [109,110]. The curcumin analogs were obtained from the Claisen-Schmidt condensation of substituted 3-phenyl-ketone and various aromatic aldehydes. By using the ELISA technique, the designed analogs of curcumin were tested for their *in vitro* anti-inflammatory effects in mouse peritoneal macrophages. Active compounds (10 μmol) exhibited dose dependent anti-inflammatory activity in LPS-induced exacerbated release of TNF-α and IL-6 and showed high chemical stability confirmed by UV absorption spectra. From the data it was observed, that

compounds, substituted by NO_2 on R_1, exhibited stronger inhibitory activity than CF_3 on R_1, while cyclohexanone contributed to potent anti-inflammatory activity of these analogs in comparison with cyclopentanone as the connecting link. Moreover, the compound with R_2 containing methoxyl and/or hydroxyl group on the phenyl ring showed better anti-inflammatory activities than their correspondence with the electron-withdrawing group. The most active compound **36** with greater than 90% inhibition rate was selected for *in vivo* studies and mechanistic evaluation was performed [110].

Bandgar *et al.* further strengthened the above-mentioned observations. A series of novel curcumin analogs by Claisen-Schmidt condensation of various aromatic and heteroaromatic amides were prepared and evaluated for anti-inflammatory effects. Results revealed that the synthesized compounds in comparison with dexamethasone have shown excellent inhibition of TNF-α (91–83%) and in case of IL-6 (98–95%). Among the series, compound **37** (1 mM) was the most active against experimental model. Structure elucidation in terms of biological activity revealed that compounds containing electron-withdrawing substituent on amide ring have higher TNF-α and IL-6 inhibitions than their counterpart containing electron-donating substituent on amide ring. On the other hand, compounds with fluorine and trifluoromethyl substitution on amide ring have highest activity [79].

Another study documented the anti-inflammatory potential of newly synthesized 26 asymmetric monocarbonyl analogs of curcumin at three different doses (10, 5, 2.5 μmol) through the inhibition of TNF-α and IL-6 in a model of mouse RAW 264.7 macrophages stimulated by LPS (0.5 μg/ml). All the compounds presented good anti-inflammatory activity but compounds **38a, 38b, 38c, 38d** and **38e**, manifested highly significant and dose-dependent inhibition of TNF-α and IL-6. Mechanistically, this inhibition was found due to the inhibition of ERK phosphorylation and NF-κB pathway [111].

Recently, Zhang *et al.* reported unusual findings in his study conflicting to the aforesaid work that symmetric analog served as potent anti-inflammatory agents as compared with asymmetric ones. The author classified the newly synthesized 34 monocarbonyl curcumin analogs into two series symmetric monocarbonyl analogs of curcumin and asymmetric monocarbonyl analogs of curcumin. Among the analogs, the symmetrical heterocyclic type displayed the strongest inhibition against LPS-induced cytokines release in mouse macrophages. In particular, **39** with a thiopyrone structure and 4-piperidone derivative **40** showed stronger inhibition with a range of 59.5–83.4%. Further NF-κB results showed that molecular symmetry and electronegativity might play a crucial role in the anti-inflammatory activity of these monocarbonyl curcumin analogs. Mechanistically, compound **39** significantly inhibited LPS-induced phosphorylation of ERK [112].

Recently, Gazzar *et al.* synthesized a new series of symmetric curcumin analogs by keeping the 7-carbon dienone spacer between the two phenyl rings along with the substitution of the phenolic OH with different linkers hence giving additional keto-enol tautomerism. These compounds were evaluated for their anti-inflammatory effects in gamma irradiated rats through inhibition of NO, IL-6, TNF-α and NF-κB levels by using ELISA kits. It was observed that compound **41** demonstrated enhanced suppression of TNF-α and NF-κB with percentage inhibition of 69.6 and 56.4%, while compound **42** decreased serum level of IL-6 with percentage inhibition of 72.5%. Detailed SAR studies were not reported [113].

Analogously, in a model of LPS (1 μg/ml)-induced IL-6 and TNF-α release, the inhibitory effects of a series of newly synthesized symmetric monocarbonyl analogs of curcumin were evaluated *in vivo.* Overall, the analogs with cyclopentanone rings displayed good inhibitory effects on the release of these cytokines, particularly compound **43** (1, 2.5, 5.0, 10 and 20 μmol) showed significant anti-inflammatory activity in a dose-dependent manner which was attributed to the position of methoxyl group in the aromatic ring [114].

Bukhari *et al.* synthesized and examined a series of 30 novel α,β-unsaturated carbonyl based compounds for the inhibitory effects of TNF-α and IL-6 in the macrophages. The results showed that five out of 30 compounds demonstrated dose-dependent inhibition of pro-inflammatory cytokines secretion. Linear or cyclic linkers derived from the ketone between the two aromatic rings of compounds were linked to the inhibitory activities. The most potent inhibitor **(17d)** corresponded to *N*-methyl-4-piperidone and 4-piperidone moieties [3]. These compounds have also been reported as inhibitors of β-amyloid peptide aggregation and anticancer agents [115]. Recently, same class of compounds has also been documented with multiple biological characteristics including antitumor activity [116] and inhibitors of acetylcholinesterase, butyrylcholinesterase and monoamine oxidase enzymes [117,118].

Another novel series of both symmetric and asymmetric allylated monocarbonyl analogs of curcumin were prepared and investigated against TNF-α and IL-6 expression induced by LPS for both *in vitro* and *in vivo* models. ELISA kits were used for *in vitro* inhibition of pro-inflammatory cytokines and it was seen that compound **44** exhibited significant inhibition of TNF-α, IL-6 at a dose of 10 μmol with percentage inhibition of 83.26 and 43.81%, respectively. This compound was further evaluated for *in vivo* inhibitory

Table 2. Anti-inflammatory properties of curcumin analogs.

Inflammatory mediator	Functional group promoting activity	Ref.
COX1 and COX2	Pyrazole ring	[76]
	Methoxy or methyl ester group on phenyl ring	[91]
	Electron withdrawing substituent on amide ring	[79]
	Dimethoxyl group, furanyl ring and vanillin moiety	[2]
	N-methyl-4 piperidone linker	[3]
	Diethyamine group at position 4 of phenyl ring	[94]
	N-methyl-*N*-(2-hydroxyethyl)-4-amino	[94]
LOX pathway	2-methyl-*N*-ethyl-*N*-(2-cyanoethyl)-4-amino	[94]
	Heterocyclic substituent of aromatic part	[87]
	N-methyl-4 piperdone linker	[3]
iNOS	Increase no. of methoxy group and conjugated double bond	[96]
	2,5-Dimethoxylated and 2 hydroxylated phenyl rings	[99]
	Presence of hydroxy group in both rings	[100]
	5 methyl thiophenyl	[101]
NFκB	Enone analog with 5-carbon spacer	[74]
	Increase number of methoxy group	[96]
TNF-α and IL-6	Dimethyl propoxyl and alloxyl substituent	[106]
	Presence of cyclohexanone and 3-methoxyl group	[107]
	N,*N*-dimethyl propoxy substituent	[109]
	Electron withdrawing substituent on aromatic ring (2-nitro substitute compound)	[103]
	Presence of NO2 on R1 and methoxyl/hydroxyl group on R2 and cyclohexanone	[110]
	Electron withdrawing substituent on amide ring and fluorine, trifluoromethyl substituent	[79]
	Thiopyrone structure and 4 piperidone derivative	[111]

COX-1: Cyclooxygenase-1; COX-2: Cyclooxygenase-2; iNOS: Inducible nitric oxide synthase; LOX: Lipoxygenase.

activity at different doses (1, 2.5, 5, 10 μmol) in RAW macrophages and results revealed that compound **44** exhibited highly significant and dose-dependent inhibition of cytokines. Detailed SAR studies were not provided, however, it was concluded that 4-methyl piperidinyl was responsible for increased anti-inflammatory effects of this compound [119]. Figure 7 shows the structures of curcumin analogs with potential inhibitory effects on pro-inflammatory cytokines. The anti-inflammatory properties of various curcumin analogs have been summarized in Table 2.

Conclusion

Curcumin, being the multitargeting agent and with its striking antioxidant and anti-inflammatory potential seemed to be involved in the treatment of various diseases. Extensive research on curcumin and its natural and synthetic analogs, over the past few decades has endorsed its resiliency and plausibility for alteration of structural features. In this review, we summarized all those novel synthetic analogs considering the updated research outcomes that exhibit the anti-inflammatory and antioxidant effects by inhibiting the several inflammatory mediators and causing free radical scavenging. According to the experimental studies both *in vitro* and *in vivo* carried out by recent-age scientists, the presence of different functional entities found to be responsible for antioxidant property include methoxy, phenoxy and carbon–carbon double bonds. However, the remarkable anti-inflammatory property was associated with the symmetry of structure, position of substituents along with the number of methoxy groups. In addition, electron withdrawing substituents and α,β-unsaturated carbonyl group was indicated imperative for reactivity.

Future perspective

The structural design of this multitargeting agent has been an emergent area of interest till now since a great

number of compounds have been developed in the past decades. This review of literature provides an insight into curcumin analogs with the most potent analogs to be investigated against inflammatory diseases. It is expected that these analogs are further explored to find their role in multiple biological activities and chronic pathological conditions in addition to stimulate the researchers to look for new synthetic curcumin entities in order to overcome the limitations and improve the efficacy of curcumin.

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Executive summary

Inflammation & oxidative stress

- Inflammation is a defensive response of human body system triggered through either immune mechanism or nonimmune mechanism. The unabating inflammatory process and peroxidation of membrane lipids through free radical formation is considered to be associated with the root cause of many inflammatory diseases and chronic pathological conditions.

Curcumin as an anti-inflammatory agent

- Curcumin has been reported to be involved in the treatment of various chronic inflammatory diseases through the inhibition of important enzymes involved in arachidonic acid metabolism pathway like secretory PLA_2, COX-1, COX-2, LOX along with the iNOS and pro inflammatory cytokines, regulating the process of inflammation.

Conclusion

- Since the past few decades, a number of synthetic curcumin analogs have been extensively studied for anti-inflammatory and antioxidant effects.
- The review of literature revealed that methoxy, phenoxy and carbon–carbon double bonds are responsible for antioxidant activities while α,β-unsaturated carbonyl group along with electron withdrawing substituents, position of substituents and symmetry of structure is directed as obligatory for reactivity.

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