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Review Article

Recent Development in the Structural Modifications of Monocarbonyl Analogues of Curcumin and their Improved Biological Activities: A Review

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ABSTRACT

Curcumin is a polyphenolic constituent of the rhizome of *Curcuma longa* and is known for its versatile biological properties like antioxidant, anti-bacterial, anti-cancer, anti-inflammatory, antiviral and so forth. Despite possessing a wide range of reported pharmacological effects, its clinical applicability is restricted, because of the poor bioavailability and poor solubility due to the presence of β-diketone moiety in its structure. Several strategies have been developed in the past decade to overcome this disadvantage. One important approach is designing and synthesizing new curcumin derivatives which have improved therapeutic properties and bioavailability than curcumin. Therefore, Monocarbonyl Analogues of Curcumin (MACs) have been synthesized with improved physiological properties and pharmacological effects. There is also a continued interest in synthesizing analogues that should have almost identical safety profiles like curcumin, but increased activity with enhanced oral bioavailability. This review describes the recent development in the structure modification of MACs and focuses on their anti-oxidant, antibacterial, anticancer activities and other biological activities.

Keywords: Monocarbonyl analogues, Curcumin, Antioxidant, Antibacterial, Anticancer.

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INTRODUCTION

Both tradition and science have been utilized by various communities around the world for discovering food and plants that can prevent and treat various diseases. Turmeric is a member of ginger family and is used on a large scale to preserve food mainly in south-west Asia and due to its diverse pharmacological properties, it is traditionally used for treating different diseases.[1] Curcumin or diferuloylmethane is an essential component of turmeric (*Curcuma longa*), which gives it a yellow colour and exhibits various biological activities. Some of its pharmacological activities and medicinal properties, that have been reported, include: antioxidant,[2-4] anti-proliferative,[5] anti-inflammatory,[6] anti-cancer,[7-9] and anti-bacterial Figure 1.[10] Studies on curcumin revealed that it could be taken up to 12 g/day, without showing any toxicity in humans.[11] The curcumin has gained the interest of clinicians due to its ability to interact with numerous molecular and biochemical targets such as transcriptional factors, inflammatory cytokines, kinases, receptors, enzymes, growth factors, and ligands therefore, its therapeutic potential has been explored by carrying out clinical studies. A large number of clinical trials are going on universally to discover its therapeutic potential against various diseases.[11,12] Curcumin is not considered a suitable drug, in spite of possessing such a vast majority of biological activities due to its low bioavailability and instability at certain pH conditions.[13] Several analogues have been synthesized through multiple approaches in order to overcome these limitations.[14-16]

Various research groups have displaced the β-diketone moiety responsible for the metabolic instability of curcumin with a single carbonyl group to produce monocarbonyl analogues of curcumin. Also, those MACs with electron-withdrawing groups showed better cytotoxicity.[17] From several studies over the past decade, it was also revealed that curcumin has poor absorbtion ability. It was first observed by Wahlstrom and Blennow in 1978 by using Sprague-Dawley rats. They found that after oral administration of 1 g/kg of curcumin, a negligible amount of curcumin was present in the blood plasma of rats.[18] The synthesis of monocarbonyl analogues of curcumin has been done extensively and the process is still in progress with many analogues showing good biological activities while others do not. In this review, the focus is on the

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recently synthesized MACs with several structural modifications and their improved and effective biological activities.

Antioxidant Activity of Monocarbonyl Analogues of Curcumin

Antioxidants prevent the production of free radicals during a chemical reaction. These are added in foods as a preservative to protect them from spoilage by preventing oxidation. Antioxidant acts as a reducing agent by scavenging the reactive oxygen species produced during the oxidation reaction. The reactive oxygen species can damage the cellular component of living organisms such as DNA, lipids and protein. They, however, also have some positive effects, therefore, the function of antioxidants is not to eliminate them completely, but to keep them at an optimum level.[19] A large number of monocarbonyl analogues of curcumin have been synthesized by various research groups and their antioxidant activity was studied. Li *et al.*[20] have synthesized MACs and demonstrated their activity against myocardial I/R injury which plays an important role in myocardial infarction and inhibiting ROS (Reactive Oxygen Species) is an effective strategy for its treatment. Among the synthesized MACs, (1*E*,4*E*)-1-(3-allyl-4-Methoxyphenyl)-5-(2-Chlorophenyl) penta-1,4-dien-3-one (**1**) showed the highest inhibition effect against oxidative stress (Figure 2). The MAC has the capability to minimize TBHP-induced cell apoptosis *in vitro* and protect against myocardial ischemia-reperfusion injury *in vivo*. Curcumin analogues were further investigated for their antioxidant activity in obese rats. Evidence has shown that oxidative stress and inflammation are the main factors in the development of obesity-induced cardiac disorders.[21] Qian *et al.*[22] synthesized curcumin analogue (2*E*,6*E*)-2-(2-Bromobenzylidene)-6-(2-(Trifluoromethyl)Benzylidene)Cyclohexanone **(2)** and evaluated

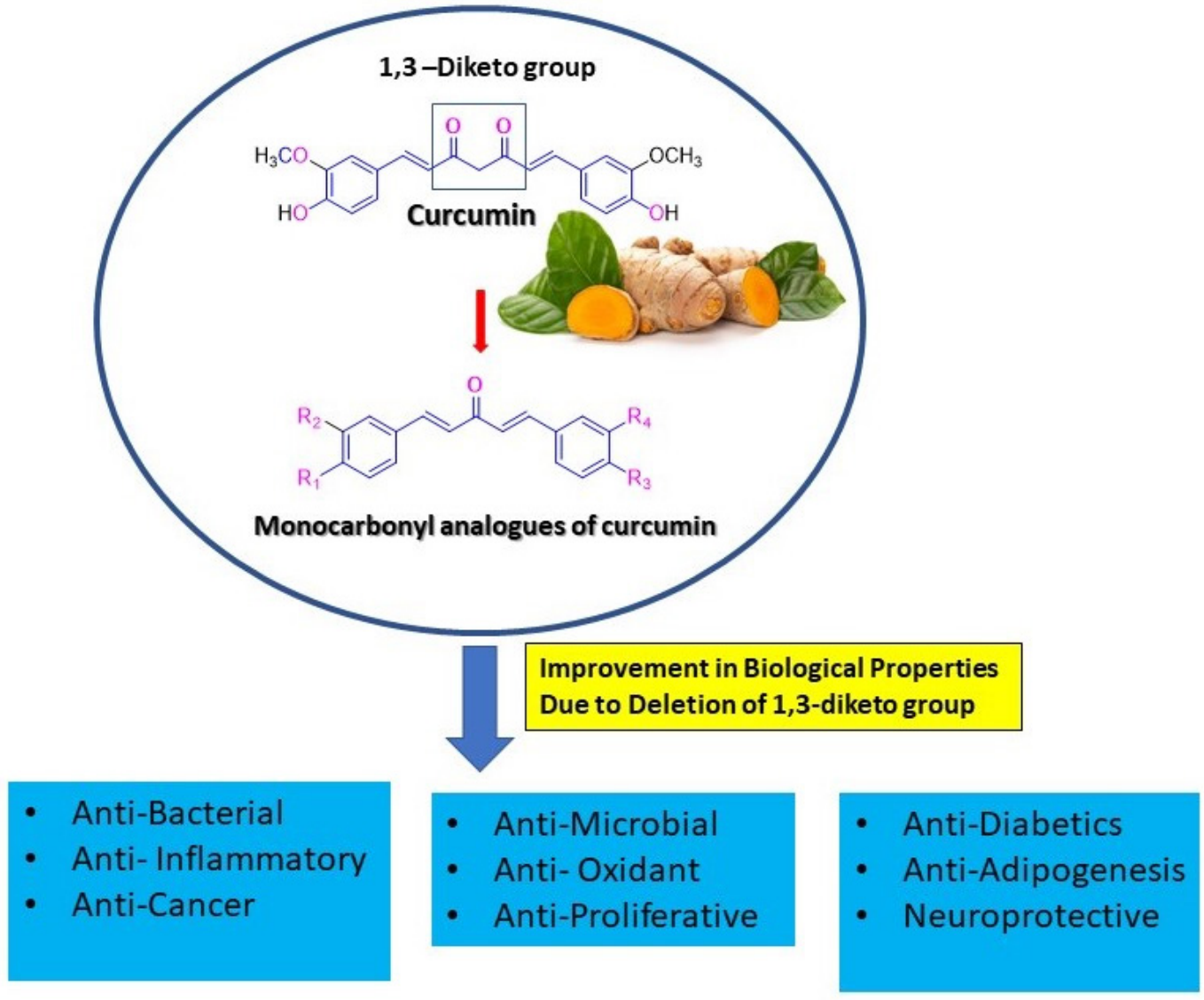

Figure 1: Structural Modification of Curcumin into more stable Monocarbonyl Analogues of Curcumin.

its effect in obese rats (Figure 2). This compound at 20 mg/kg concentration showed much better activity than curcumin at 50 mg/kg. The analogue acts by increasing the Nrf2 expression, an important transcription factor that helps in the regulation of multiple antioxidants. Similarly, Deck *et al.*[23] synthesized enone analogues of curcumin and analysed its effect towards Nrf2 activation. Analogues **3** and **4** are the most active among the synthesized analogues (Figure 2). The results have also shown that analogue **5** without any functional groups showed good activity, whereas, its reduction product **6** was not observed to be very active which confirms that enone is important for the activity of analogues.

The mechanism behind curcumin reactivity as an antioxidant agent remains controversial among scientists. Some has given more attention to the phenolic rings while others focused on the β-diketone moiety. Various research groups suggested that its free radical scavenging activity is due to the presence of phenolic groups.[24] Other have shown that the antioxidant activity of curcumin is due to H atom abstraction from the β-diketone CH_2 group.[25] Li *et al.*[26] synthesized curcumin analogues and evaluated their antioxidant activity by DPPH, ABTS, TRAP and NET radical scavenging assay *in vitro.* Among the synthesized analogues, **7** and **8** exhibited highest activity (Figure 2). The study has shown that by shortening the chain, the antioxidant activity is improved. Also, the analogues without the phenolic groups hardly showed the antioxidant activity. But the activity of analogues having OCH_3 groups is comparable to curcumin.

Hadzi-Petrushev *et al.*[27] synthesized (2*E*,6*E*)-2,6-bis(2-bromobenzylidene) cyclohexanone **9** and tested its antioxidant activity in rats with cardiac hypertrophy. Excessive ROS level is considered one of the factors associated with cardiac hypertrophy. Keeping this in mind, a beneficial therapeutic effect is to lower the ROS production or its inactivation by enhancing the cellular antioxidant system. Compound **9** displayed strong thiol prevention which can be noticed in the amount of t-SH and f-SH (total and free Sulfohydryl groups). Also, previous data suggested that electron-releasing power expressed in terms of energy of HOMO can be useful in discovering compounds having anti-inflammatory and antioxidant activities.[28] Compound **9** consists of electron-withdrawing substituents and has the capability of donating electrons because of the lower energy of HOMO and therefore can be a good candidate required for the antioxidant activity.

Nagargoje *et al.* synthesized quinoline-based monocarbonyl curcumin analogues and evaluated their antioxidant activity using a DPPH assay taking BHT (Butylated Hydroxyl Toluene) as a standard.[29] All the analogues performed better than BHT. The analogues **(10, 11, 12, 13**) with chloro substitution on quinoline exhibit threefold more antioxidant potential (Figure 2) According to the IC_{50} values, analogues with acetone as an open chain linker show a favourable rise in activity followed by cyclopentanone, cyclohexanone and N-methyl piperidone spacer. The same group synthesized propargylated monocarbonyl curcumin analogues using claisen-schmidt type condensation. Butylated Hydroxyl Toluene (BHT) was used as a standard.[30] Compound **14** with acetone linker and 3,5 chloro substitution on the aromatic ring exhibits potential antioxidant activity (IC_{50}=12.78±0.71) as compared to BHT (IC_{50}=16.47±0.18). Moreover, analogues **15**, **16**, and **17** showed higher activity or comparable to BHT (Figure 2).

Hussain *et al.* tested the antioxidant activity of the synthesized monocarbonyl curcumin analogues.[31] They did hippocampal-based study *in vivo* mouse models. Analogues **18** and **19** showed the highest antioxidant activity against DPPH radical assay (Figure 2). Similarly, the analogue **19** was found to be most effective against ABTS assay when compared to the standard drug tocopherol. The biochemical assessment of these analogues was also studied. The results showed that the synthesized analogues were able to reduce lipid peroxidation (MDA) level and increase the activity of antioxidant enzymes such as Catalase (CAT), Superoxide Dismutase (SOD), and Glutathione (GSH) by reducing the oxidative stress in the hippocampus.

Recently, hybrids of monocarbonyl curcumin and coumarin were also synthesized by Negi *et al*. using the click chemistry approach (Figure 3). These hybrids exhibited moderate antioxidant activity.[32]

Antibacterial Activity of Monocarbonyl Analogues of Curcumin

The broad study of the antibacterial properties of curcumin and its synthetic analogues has been done by Zorofchian *et al.*[33] The bacterial cells divide by assembly of a septal structure Z-ring, which consists of tubulin-like protein FtsZ as the main constituent.[34] FtsZ plays an important role in facilitating several cellular factors that help in cell division. It was shown that curcumin inhibits the assembly of FtsZ Protofilaments in *Bacillus subtilis.*[35,36] However, due to the limitations as discussed above its monocarbonyl analogues have been synthesized. Morao *et al.*[37] synthesized the simple analogue of curcumin **20** in which the β-diketone moiety was replaced with monocarbonyl and the vanillyl and double bonds remained untouched (Figure 4). The analogue was tested against Gram-positive and Gram-negative bacteria. The study indicated that compound **20** has the capability to disorganize the divisional septum of *B. subtilis*. It was effective against the plant pathogen *Xanthomonas citri* (*X. citri*), *Enterococcus faecalis* (*E. faecalis*) and the Gram-positive bacteria *Bacillus subtilis* (*B. subtilis*). The simplified analogue showed 60 to 75% growth inhibition against *E. faecalis* which is resistant to many antibiotics. The study has also shown that the synthetic analogue requires 90 min to completely disorder the septum of *B. subtilis.* However, it was also seen that there was no sign of morphological damage or stress.

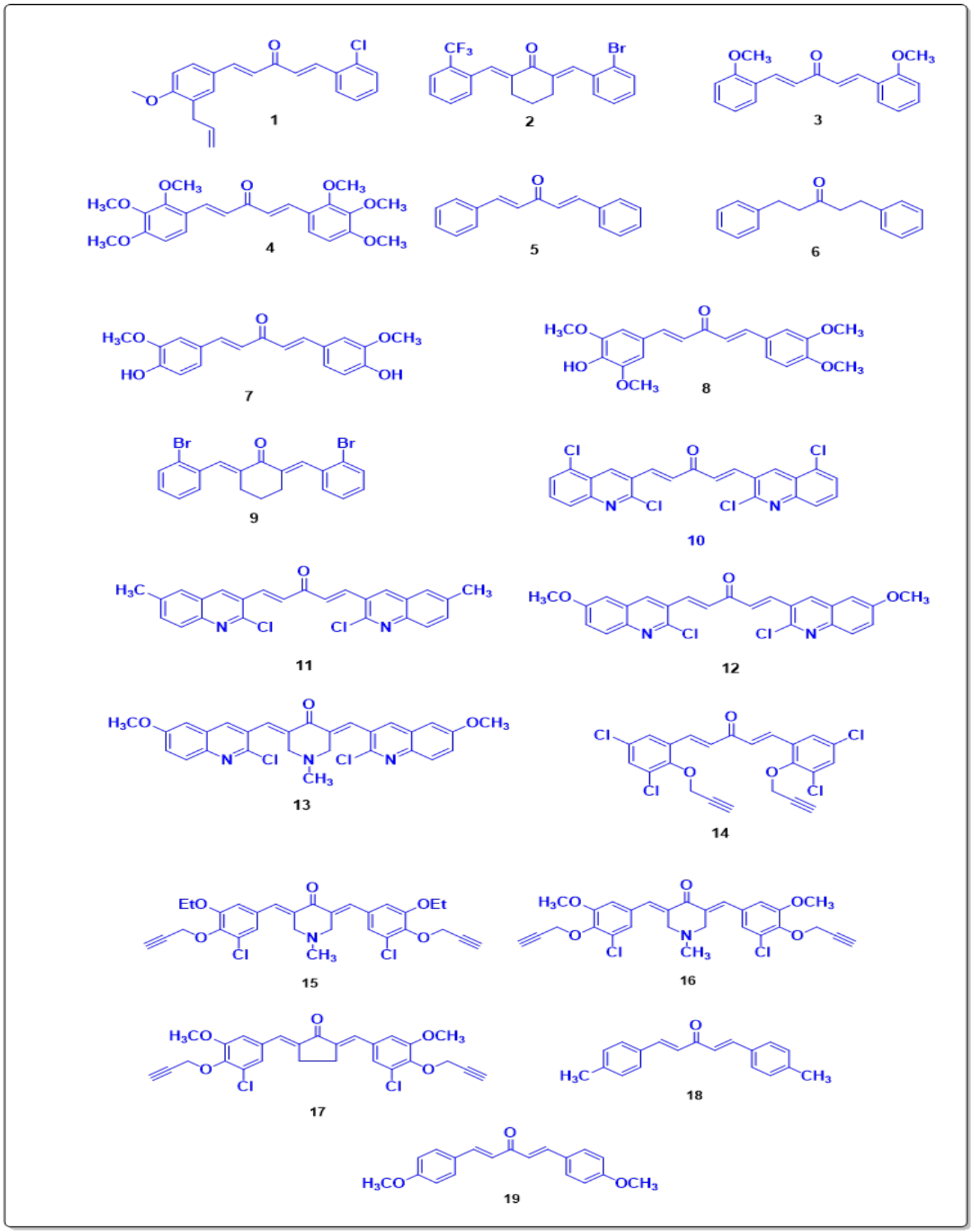

Figure 2: Structures of Monocarbonyl Analogues of Curcumin showing Antioxidant Properties.

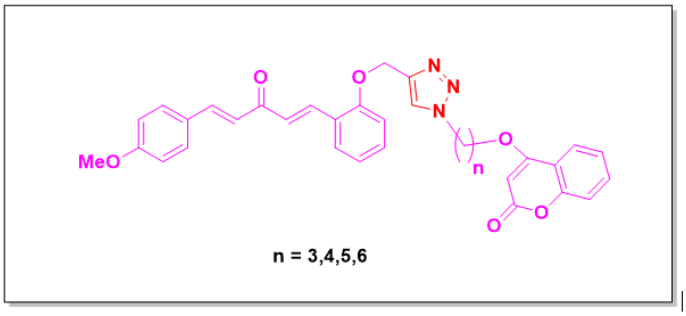

Figure 3: Structure of Monocarbonyl Curcumin-Coumarin Hybrids.

Polaquini *et al.*[38] synthesized unsymmetrical MACs and examined their antibacterial activity against Gram-positive and Gram-negative bacteria. Among the synthesized analogues **21, 22** and **23** showed the broad spectrum and potent activity against *Acinetobacter baumannii* and Methicillin-Resistance *Staphylococcus Aureus* (MRSA), with MIC (Minimum Inhibitory Concentration) values ranging from 0.9 to 15.6 µg/mL (Figure 4). The analogues were also evaluated based on their structures by changing the position of the methoxy and hydroxyl groups on the aromatic ring of curcumin. From the results obtained, it was suggested that the meta position was more suitable for antibacterial activity. Also, the analogues were more selective and less toxic towards the healthy cells. Kumar *et al.*[39] synthesized more stable monocarbonyl curcuminoids and tested them against *S. aureus*. Many strains of *S. aureus* have become resistant to drugs and are therefore considered as Multi-Drug Resistant (MDR) bacteria. The curcuminoids **24**, **25**, **26**, **27**, **28** and **29** were found to exhibit good antibacterial activity against MRSA (Methicillin-resistant *S. Aureus*) and MSSA (Methicillin-Sensitive *S. Aureus)* (Figure 4). Their MIC values were in the range of 16-32 µg/mL compared to curcumin which remains inactive even at the concentration of 256 µg/mL. Another monocarbonyl analogue 1,5-bis (3'-ethoxy-4'-hydroxyphenyl)-1,4-pentadiene-3-one (**30**) was synthesized by Purwanggana *et al.* (Figure 4).[40] It exhibits better anti-bacterial activity than the antibiotics amoxicillin and cefadroxil against *S. aureus, S. epidermidis* (Gram-positive) and *Escherichia coli, Salmonella thypi* (Gram-negative).

The Minimum Inhibitory Concentration (MIC) for the analogue was 0.14 (ppm) for all the test bacteria while it is greater than one for amoxicillin and cefadroxil. The researcher suggested that due to the large lipophilicity of the analogue, it can diffuse in cell walls of gram-negative bacteria that comprise of phospholipids, lipoproteins and lipopolysaccharides. Also, due to the steric properties of the analogue, it can put pressure on gram-positive bacteria which causes cell lysis and ultimately the death of the microbial cells. A novel EF24 dimer (**31**) linked via Diethylenetriaminepentacetic Acid (DTPA) known as EF_2DTPA (**32**) was synthesized and evaluated for antibacterial activities by Vilekar *et al.*[41] The dimer was found to be most effective for the bacteria *E. coli* as compared to *E. faecalis* and *S. aureus*. Zhang *et al.*[42] synthesized a series of analogues attached with benzotriazin4(3H)one moiety. Recently it was studied that benzotriazin4(3H)one showed good nematicidal activity. The results obtained after combining monocarbonyl analogue with benzotriazin4(3H) showed that these analogues **33a-33i** exhibited enhanced antibacterial activities against *Xanthomonas axonopodis pv. citri* (*Xac*) and *Ralstonia solanacearum* (*Rs*) *in vitro*. Among these analogues, **33b** and **33f** exhibited the highest antibacterial activity with EC_{50} values of 22.45 (*Xac*) and 34.77 (*Rs*) µg/mL (Figure 4).

Anticancer Activity of Monocarbonyl Analogues of Curcumin

A large number of MACs have been synthesized which exhibits good and better anticancer activity than curcumin. The medicinal plants consist of different types of anticancer compounds and exploration of their pharmacological and chemical properties are in progress.[43,44] Weng *et al.*[45] synthesized long-chain alkoxylated MACs and evaluated them for anticancer activity in gastrointestinal cancer cells The compounds that showed the highest inhibitory activity were **34**, **35** and **36**. These compounds showed the ability to upregulate cleaved Poly ADP-ribose Polymerase (PARP) and downregulate the expression of caspase-3 and Bcl-2 in SGC-7901 cells, while these effects were not shown by the curcumin. Similarly, Qiu *et al.*[46] synthesized allylated monocarbonyl analogues and evaluated them against liver cancer cells HUCCA, QBC-939 and RBE. The compound **37** exhibited significant cytotoxicity (8.7 µM in HUCCA cells, 9.3 µM in QBC939 cells, and 8.9 µM in RBE cells). Hence, this compound can be further useful in the treatment of liver cancer. Similarly, the curcumin analogues synthesized by Pignanelli *et al.*[47] have shown anticancer activity in human cancer cells, which includes triple-negative, inflammatory breast cancer cells. MACs **38** and **39** were found to be the most potent and induces apoptosis in different cancer cells with minimum damage in normal cells. It was suggested that these analogues decrease the expression of BCl-2 protein which was overexpressed in cancer cells (Figure 5).

Twenty curcumin analogue hybrids were synthesized and their anticancer activity was tested against human gastric cancer cell (SGC-7901, MGC-803), human liver cancer cells (SMMC-7721), and human glioma cell (U87).[48] Gastric cancer cell apoptosis was induced by compound **40** which exhibited highest activity by arresting the cell cycle, inhibiting TrxR activity and breaking mitochondria function. Thioredoxin Reductase (TrxR) is involved in the signalling pathway and it is overexpressed in many human cancer cells. The IC_{50} inhibitory value against TrxR was found to be 0.783 µM. A curcumin analogue WZ35 (**41**) was found to inhibit the glycolysis in gastric cancer cells through the ROS-YAP-JNK pathway.[49] The results obtained showed that WZ35 was able to inhibit the proliferation of gastric cancer cells, and alter glycolysis-related proteins like G6PD, *p* GSK3α, PDHK1, *p* GSK3β and thus regulate glycolysis through inhibition of the proliferation of gastric cancer. Recently, asymmetric MACs

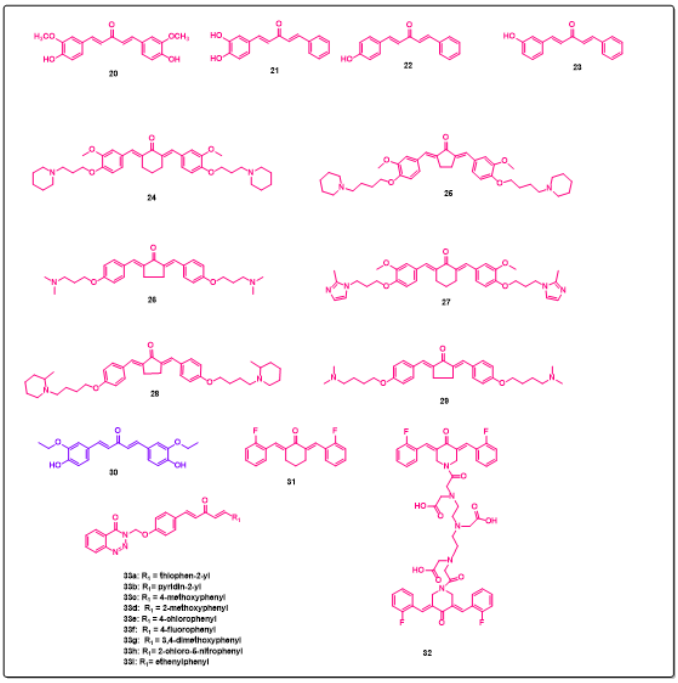

Figure 4: Monocarbonyl Analogues of Curcumin showing Antibacterial Activities.

fused with 1H-pyrazole were synthesized and their anticancer activity was evaluated in breast cancer cell MDA-MB-231 and liver cancer cells HepG2.[50] Analogues **42**, **43** and **44** exhibited strong cytotoxicity (IC_{50} 3.64–5.61 μM) towards MDA-MB-231. These compounds were found to exhibit strong inhibition on tubulin polymerization (40.76–52.03%) and as a consequence were further examined for their cellular effects on breast cancer cells (Figure 5).

Other Biological Activities of Monocarbonyl Analogues of Curcumin

da Silva *et al.*[51] reported the antiparasitic activity of synthetic monocarbonyl analogues against the parasite *Trichomonas vaginalis*. Among the twenty-one synthetic analogues tested, two derivatives of propanone (**45** and **46**) and one cyclohexanone derivative (**47**) showed comparable anti-T. vaginalis activity to the standard drug metronidazole, at the concentrations examined with MIC values 80, 90 and 200 μM respectively (Figure 6). The synthetic analogues that were designed exhibited lower effective concentrations compared to the natural parent compound curcumin. This suggests that conducting additional studies with this group of compounds would be valuable, as these analogues have the potential to be explored as viable alternatives for treating trichomoniasis and other parasitic infections. du Preez *et al.*[52] studied the application of new monocarbonyl curcumin analogues against tuberculosis. Additionally, they investigate to determine the relationship between the activity and chemical structure of these compounds. The standout compound (**48**) displays remarkable antitubercular activity against

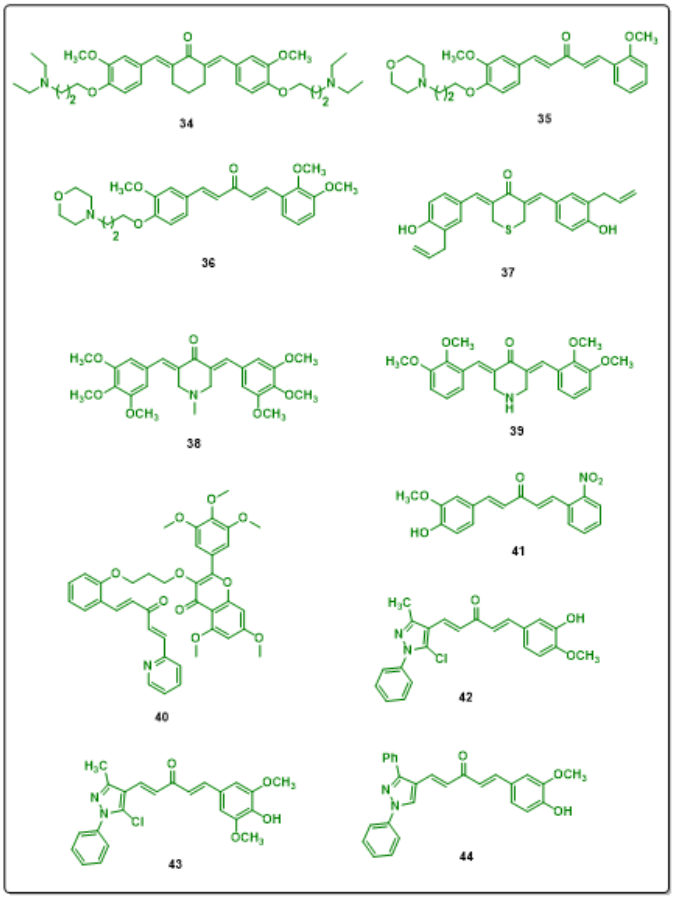

Figure 5: Structure of Monocarbonyl Analogues of Curcumin having Anticancer Activities.

Mycobacterium tuberculosis (M.tb) with MIC90 values ranging from 0.2 to 0.9 μM in both ADC and CAS media. Nagargoje *et al.*[29] synthesized novel 2-chloroquinoline-based monocarbonyl analogues of curcumin (MACs). The MACs were tested for the antioxidant and antifungal activity *in vitro*. Five different fungal strains, *Aspergillus Flavus, Fusarium Oxysporum, Cryptococcus neoformans Candida albicans*, and *Aspergillus Niger* were used for determining their activity. Among all the synthesized compounds **49** and **50** were highly effective against all fungal strains. The MIC (μg/mL) values for **48** against the above-mentioned fungal strains are 12.5, 12.5, 25, 25 and 12.5 and for **49** are 6.25, 25, 12, 25 and 12.5 respectively (Figure 6). Hussain *et al.*[53] synthesized and tested five mono-carbonyl curcumin analogues and evaluated their anticholinesterase activities *in vitro*. Among five analogues, **51** and **52** showed significantly higher memory-enhancing effects (Figure 6). Matiadis *et al.*[54] group developed and synthesized ten hydroxylated monocarbonyl curcumin derivatives, and then assessed their ability to upregulate NEP (Neprilysin) using fluorescence-based assays that are sensitive to Aβ (Amyloid beta) digestion and inhibition. Among the ten analogues tested, Compound **53** demonstrated the highest level of activity, leading to a notable 50% increase in Aβ cleavage activity (Figure 6).

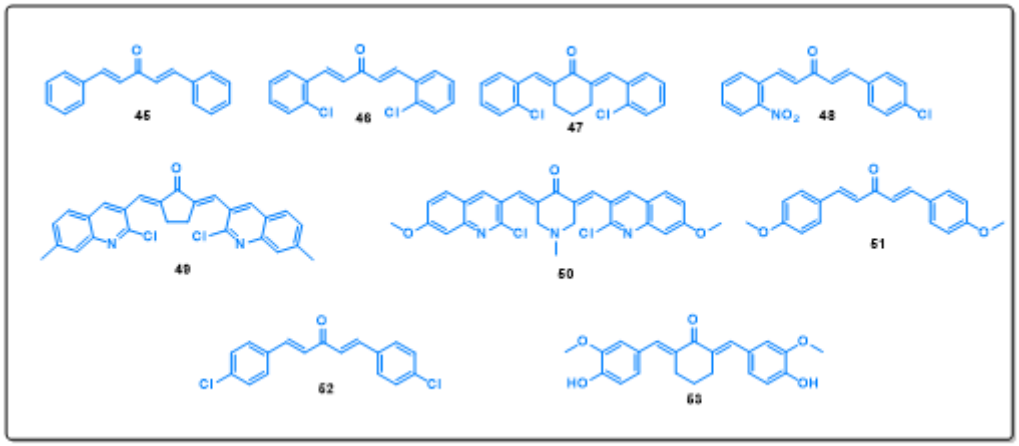

Figure 6: Structure of Monocarbonyl Analogues with Miscellaneous Biological Activities.

CONCLUSION

Curcumin exhibited good antioxidant, anticancer, anti-inflammatory, antimicrobial activities etc. However, it has not been accepted as a drug because of the poor bioavailability and solubility. To address this issue, several approaches have been adapted to get control of this limitation. One of the important methods that is used to improve curcumin biological properties is synthesizing the Monocarbonyl Analogues of Curcumin (MACs) which are obtained after deleting its β-diketone moiety. As evident from the above literature, the Monocarbonyl Analogues of Curcumin (MACs) have improved physical properties and exhibits good to excellent biological activities when compared to curcumin. It was also suggested that by changing the substituents on the aromatic ring, effected the biological properties of curcumin. Overall, from the studies conducted on curcumin, one can conclude that curcumin is a promising molecule which can be used for designing and synthesizing new effective compounds which can prove to be beneficial in treatment of various diseases that are threatening the human lives.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MACs: Monocarbonyl analogues of curcumin; **Nrf2:** Nuclear factor erythroid 2-related factor 2; **TrxR:** Thioredoxin reductase; **IC_{50}:** Inhibitory Concentration 50; **ROS:** Reactive Oxygen Species; **DPPH:** α, α-Diphenyl-β-picrylhydrazyl; **ABTS:** 2,2-Azino-Bis-3-ethylbenzothiazoline-6-sulphonic acid; **TRAP:** Total Reactive Antioxidant Potential; **MDR:** Multidrug Resistant; **FtsZ:** Filamenting temperature-sensitive mutant Z; **MIC:** Minimum Inhibitory Concentration.

REFERENCES

1. Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, *et al.* Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. Biochem Pharmacol. 2008;76(11):1590-611. doi: 10.1016/j.bcp.2008.08.008, PMID 18775680.
2. Kelkel M, Jacob C, Dicato M, Diederich M. Potential of the dietary anti-oxidants resveratrol and curcumin in prevention and treatment of hematologic malignancies. Molecules. 2010;15(10):7035-74. doi: 10.3390/molecules15107035, PMID 20944521.
3. Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, *et al.* Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. Carcinogenesis. 2007;28(8):1765-73. doi: 10.1093/carcin/bgm123, PMID 17522064.
4. Balogun E, Hoque M, Gong P, Killeen E, Green CJ, Foresti R, *et al.* Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. Biochem J. 2003;371(3):887-95. doi: 10.1042/BJ20021619, PMID 12570874.
5. Reuter S, Eifes S, Dicato M, Aggarwal BB, Diederich M. Modulation of anti-apoptotic and survival pathways by curcumin as a strategy to induce apoptosis in cancer cells. Biochem Pharmacol. 2008;76(11):1340-51. doi: 10.1016/j.bcp.2008.07.031, PMID 18755156.
6. Teiten MH, Eifes S, Reuter S, Duvoix A, Dicato M, Diederich M. Gene expression profiling related to anti-inflammatory properties of curcumin in K562 leukemia cells. Ann N Y Acad Sci. 2009;1171(1):391-8. doi: 10.1111/j.1749-6632.2009.04890.x, PMID 19723081.
7. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. Advances in Experimental Medicine and Biology; 2007:105-25. doi: 10.1007/978-0-387-46401-5_3, PMID 17569207.
8. Hr TC, Chen J, Huang CY, Guan JY, Lu SH, Pu YS. Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing p21WAF1/CIP1 and C/EBPβ expressions and suppressing NF-κB activation. Prostate. 2002;51(3):211-8. doi: 10.1002/pros.10089, PMID 11967955.
9. Lev-Ari S, Strier L, Kazanov D, Madar-Shapiro L, Dvory-Sobol H, Pinchuk I, *et al.* Celecoxib and curcumin synergistically inhibit the growth of colorectal cancer cells. Clin Cancer Res. 2005;11(18):6738-44. doi: 10.1158/1078-0432.CCR-05-0171, PMID 16166455.
10. Liang G, Yang S, Jiang L, Zhao Y, Shao L, Xiao J, *et al.* Synthesis and anti-bacterial properties of mono-carbonyl analogues of curcumin. Chem Pharm Bull (Tokyo). 2008;56(2):162-7. doi: 10.1248/cpb.56.162, PMID 18239300.
11. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "curecumin": from kitchen to clinic. Biochem Pharmacol. 2008;75(4):787-809. doi: 10.1016/j.bcp.2007.08.016, PMID 17900536.
12. Hsu CH, Cheng AL. Clinical studies with curcumin. 2007;595:47180. doi: 10.1007/978-0-387-46401-5_21, PMID 17569225.
13. Sharma RA, Steward WP, Gescher AJ. The molecular targets and therapeutic uses of curcumin in health and disease. Adv Exp Med Biol. 2007;595:453-70. doi: 10.1007/978-0-387-46401-5_20, PMID 17569224.
14. Zhang Q, Zhong Y, Yan LN, Sun X, Gong T, Zhang ZR. Synthesis and preliminary evaluation of curcumin analogues as cytotoxic agents. Bioorg Med Chem Lett. 2011;21(3):1010-4. doi: 10.1016/j.bmcl.2010.12.020, PMID 21215629.

15. Lin L, Shi Q, Nyarko AK, Bastow KF, Wu CC, Su CY, *et al.* Antitumor agents. 250. Design and synthesis of new curcumin analogues as potential anti-prostate cancer agents. J Med Chem. 2006;49(13):3963-72. doi: 10.1021/jm051043z, PMID 16789753.
16. Youssef D, Nichols CE, Cameron TS, Balzarini J, De Clercq E, Jha A. Design, synthesis, and cytostatic activity of novel cyclic curcumin analogues. Bioorg Med Chem Lett. 2007;17(20):5624-9. doi: 10.1016/j.bmcl.2007.07.079, PMID 17768050.
17. Liang G, Shao L, Wang Y, Zhao C, Chu Y, Xiao J, *et al.* Exploration and synthesis of curcumin analogues with improved structural stability both *in vitro* and *in vivo* as cytotoxic agents. Bioorg Med Chem. 2009;17(6):2623-31. doi: 10.1016/j.bmc.2008.10.044, PMID 19243951.
18. Wahlström B, Blennow G. A study on the fate of curcumin in the rat. Acta Pharmacol Toxicol (Copenh). 1978;43(2):86-92. doi: 10.1111/j.1600-0773.1978.tb02240.x, PMID 696348.
19. Wolf G. The discovery of the antioxidant function of vitamin E: the contribution of Henry A. Mattill. J Nutr. 2005;135(3):363-6. doi: 10.1093/jn/135.3.363, PMID 15735064.
20. Li W, Wu M, Tang L, Pan Y, Liu Z, Zeng C, *et al.* Novel curcumin analogue 14p protects against myocardial ischemia reperfusion injury through Nrf2-activating anti-oxidative activity. Toxicol Appl Pharmacol. 2015;282(2):175-83. doi: 10.1016/j.taap.2014.12.001, PMID 25497288.
21. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm. 2010; 2010:535918. doi: 10.1155/2010/535918, PMID 20847813.
22. Qian Y, Zhong P, Liang D, Xu Z, Skibba M, Zeng C, *et al.* A newly designed curcumin analog Y20 mitigates cardiac injury via anti-inflammatory and anti-oxidant actions in obese rats. PLOS ONE. 2015;10(3):e0120215. doi: 10.1371/journal.pone.0120215, PMID 25786209.
23. Deck LM, Hunsaker LA, Vander Jagt TA, Whalen LJ, Royer RE, Vander Jagt DL. Activation of anti-oxidant Nrf2 signaling by enone analogues of curcumin. Eur J Med Chem. 2018;143:854-65. doi: 10.1016/j.ejmech.2017.11.048, PMID 29223100.
24. Sreejayan N, Rao MN. Free radical scavenging activity of curcuminoids. Arzneim Forsch. 1996;46(2):169-71. PMID 8720307.
25. Hanne HT, Greenhill JV. Studies on curcumin and curcuminoids. XXII: Curcumin as a reducing agent and as a radical scavenger. Int J Pharm. 1992;87(1-3):79-87. doi: 10.1016/0378-5173(92)90230-Y.
26. Li Q, Chen J, Luo S, Xu J, Huang Q, Liu T. Synthesis and assessment of the antioxidant and antitumor properties of asymmetric curcumin analogues. Eur J Med Chem. 2015;93:461-9. doi: 10.1016/j.ejmech.2015.02.005, PMID 25728027.
27. Hadzi-Petrushev N, Bogdanov J, Krajoska J, Ilievska J, Bogdanova-Popov B, Gjorgievska E, *et al.* Comparative study of the antioxidant properties of monocarbonyl curcumin analogues C66 and B2BrBC in isoproteranol induced cardiac damage. Life Sci. 2018;197:10-8. doi: 10.1016/j.lfs.2018.01.028, PMID 29391192.
28. Zoete V, Rougée M, Dinkova-Kostova AT, Talalay P, Bensasson RV. Redox ranking of inducers of a cancer-protective enzyme via the energy of their highest occupied molecular orbital. Free Radic Biol Med. 2004;36(11):1418-23. doi: 10.1016/j.freeradbiomed.2004.03.008, PMID 15135178.
29. Nagargoje AA, Akolkar SV, Siddiqui MM, Subhedar DD, Sangshetti JN, Khedkar VM, *et al.* Quinoline based monocarbonyl curcumin analogs as potential antifungal and antioxidant agents: synthesis, bioevaluation and molecular docking study. Chem Biodivers. 2020;17(2):e1900624. doi: 10.1002/cbdv.201900624, PMID 31863703.
30. Nagargoje AA, Akolkar SV, Subhedar DD, Shaikh MH, Sangshetti JN, Khedkar VM, *et al.* Propargylated monocarbonyl curcumin analogues: synthesis, bioevaluation and molecular docking study. Med Chem Res. 2020;29(10):1902-13. doi: 10.1007/s00044-020-02611-7.
31. Hussain H, Ahmad S, Shah SWA, Ullah A, Rahman SU, Ahmad M, *et al.* Synthetic mono-carbonyl curcumin analogues attenuate oxidative stress in mouse models. Biomedicines. 2022;10(10):2597. doi: 10.3390/biomedicines10102597, PMID 36289859.
32. Negi N, Chand G, Gahtori R, Upadhyay SK, Joshi P. Synthesis, antioxidant, and antibacterial potential of new curcumin-coumarin hybrids. Indian J Heterocycl Chem. 2023;33:1-7. doi: 10.59467/IJHC.2023.33.1.
33. Moghadamtousi SZ, Kadir HA, Hassandarvish P, Tajik H, Abubakar S, Zandi K. A review on antibacterial, antiviral, and antifungal activity of curcumin. BioMed Res Int. 2014; 2014:Article ID 186864. doi: 10.1155/2014/186864, PMID 24877064.
34. Lutkenhaus J. Assembly dynamics of the bacterial MinCDE system and spatial regulation of the Z ring. Annu Rev Biochem. 2007;76:539-62. doi: 10.1146/annurev.biochem.75.103004.142652, PMID 17328675.
35. Hurley KA, Santos TM, Nepomuceno GM, Huynh V, Shaw JT, Weibel DB. Targeting the bacterial division protein FtsZ. J Med Chem. 2016;59(15):6975-98. doi: 10.1021/acs.jmedchem.5b01098, PMID 26756351.
36. Rai D, Singh JK, Roy N, Panda D. Curcumin inhibits FtsZ assembly: an attractive mechanism for its antibacterial activity. Biochem J. 2008;410(1):147-55. doi: 10.1042/BJ20070891, PMID 17953519.
37. Morão LG, Polaquini CR, Kopacz M, Torrezan GS, Ayusso GM, Dilarri G, *et al.* A simplified curcumin targets the membrane of *Bacillus subtilis*. MicrobiologyOpen. 2019;8(4):e00683. doi: 10.1002/mbo3.683, PMID 30051597.
38. Polaquini CR, Marques BC, Ayusso GM, Morão LG, Sardi JCO, Campos DL, *et al.* Antibacterial activity of a new Monocarbonyl Analog of Curcumin MAC 4 is associated with divisome disruption. Bioorg Chem. 2021;109:104668. doi: 10.1016/j.bioorg.2021.104668, PMID 33601139.
39. Kumar P, Kandi SK, Manohar S, Mukhopadhyay K, Rawat DS. Monocarbonyl curcuminoids with improved stability as antibacterial agents against *Staphylococcus aureus* and their mechanistic studies. ACS Omega. 2019;4(1):675-87. doi: 10.1021/acsomega.8b02625.
40. Purwanggana AG, Mumpuni ES, Mulatsari ES. *In vitro* and *in silico* antibacterial activity of 1, 5-bis (3' -ethoxy-4' -hydroxyphenyl)-1, 4-pentadiene-3-one. Int J Pharm Pharm Sci. 2018;10(5):71-6. doi: 10.22159/ijpps.2018v10i5.25143.
41. Vilekar P, King C, Lagisetty P, Awasthi V, Awasthi S. Antibacterial activity of synthetic curcumin derivatives: 3, 5-bis (benzylidene)-4-piperidone (EF24) and EF24-dimer linked via diethylenetriaminepentacetic acid (EF 2 DTPA). Appl Biochem Biotechnol. 2014;172(7):3363-73. doi: 10.1007/s12010-014-0741-5, PMID 24532443.
42. Zhang JP, Li Q, Zhang C, Li P, Chen LJ, Wang YH, *et al.* Synthesis, antibacterial, and antiviral activities of novel penta-1,4-dien-3-one derivatives containing a benzotriazin-4 (3 H)-one moiety. Chem Pap. 2018;72(9):2193-202. doi: 10.1007/s11696-018-0422-x.
43. Zhang G, Ye X, Ji D, Zhang H, Sun F, Shang C, *et al.* Inhibition of lung tumor growth by targeting EGFR/VEGFR-Akt/NF-κB pathways with novel theanine derivatives. Oncotarget. 2014;5(18):8528-43. doi: 10.18632/oncotarget.2336, PMID 25138052.
44. Scotece M, Conde J, Abella V, Lopez V, Pino J, Lago F, *et al.* New drugs from ancient natural foods. Oleocanthal, the natural occurring spicy compound of olive oil: a brief history. Drug Discov Today. 2015;20(4):406-10. doi: 10.1016/j.drudis.2014.10.017, PMID 25448758.
45. Weng Q, Fu L, Chen G, Hui J, Song J, Feng J, *et al.* Design, synthesis, and anticancer evaluation of long-chain alkoxylated mono-carbonyl analogues of curcumin. Eur J Med Chem. 2015;103:44-55. doi: 10.1016/j.ejmech.2015.08.036, PMID 26318057.
46. Qiu C, Hu Y, Wu K, Yang K, Wang N, Ma Y, *et al.* Synthesis and biological evaluation of allylated mono-carbonyl analogues of curcumin (MACs) as anti-cancer agents for cholangiocarcinoma. Bioorg Med Chem Lett. 2016;26(24):5971-6. doi: 10.1016/j.bmcl.2016.10.080, PMID 27825763.
47. Pignanelli C, Ma D, Noel M, Ropat J, Mansour F, Curran C, *et al.* Selective targeting of cancer cells by oxidative vulnerabilities with novel curcumin analogs. Sci Rep. 2017;7(1):1105. doi: 10.1038/s41598-017-01230-4, PMID 28439094.
48. Wang JQ, Wang X, Wang Y, Tang WJ, Shi JB, Liu XH. Novel curcumin analogue hybrids: synthesis and anticancer activity. Eur J Med Chem. 2018;156:493-509. doi: 10.1016/j.ejmech.2018.07.013, PMID 30025345.
49. Chen T, Zhao L, Chen S, Zheng B, Chen H, Zeng T, *et al.* The curcumin analogue WZ35 affects glycolysis inhibition of gastric cancer cells through ROS-YAP-JNK pathway. Food Chem Toxicol. 2020;137:111131. doi: 10.1016/j.fct.2020.111131, PMID 31958483.
50. Doan NQH, Nguyen NTK, Duong VB, Nguyen HTT, Vong LB, Duong DN, *et al.* Synthesis, biological evaluation, and molecular modeling studies of 1-Aryl-1 H-pyrazole-fused curcumin analogues as anticancer agents. ACS Omega. 2022;7(38):33963-84. doi: 10.1021/acsomega.2c02933, PMID 36188331.
51. Carapina da Silva C, Pacheco BS, das Neves RN, Dié Alves MS, Sena-Lopes Å, Moura S, *et al.* Antiparasitic activity of synthetic curcumin monocarbonyl analogues against *Trichomonas vaginalis*. Biomed Pharmacother. 2019;111:367-77. doi: 10.1016/j.biopha.2018.12.058, PMID 30594049.
52. du Preez C, Legoabe LJ, Jordaan A, Jesumoroti OJ, Warner DF, Beteck RM. Arylnitro monocarbonyl curcumin analogues: synthesis and *in vitro* antitubercular evaluation. Chem Biol Drug Des. 2023;101(3):717-26. doi: 10.1111/cbdd.14174, PMID 36350112.
53. Hussain H, Ahmad S, Shah SWA, Ghias M, Ullah A, Rahman SU, *et al.* Neuroprotective potential of synthetic mono-carbonyl curcumin analogs assessed by molecular docking studies. Molecules. 2021;26(23):7168. doi: 10.3390/molecules26237168, PMID 34885751.
54. Matiadis D, Ng ST, Chen EH, Nigianni G, Vidali VP, Canko A, *et al.* Synthesis and biological evaluation of hydroxylated monocarbonyl curcumin derivatives as potential inducers of neprilysin activity. Biomedicines. 2021;9(8):955. doi: 10.3390/biomedicines9080955, PMID 34440159.

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