Curcumin: A Mini Review on its Synthetic Derivatives

Mohd. Javed Naim[1] & Adil Ahamad[2] & Esra Tariq Anwer[3] & Abdul Samad Salahuddin[4]

[1,4]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Tishk International University, Erbil, Kurdistan Region, Iraq
[2]Department of Pharmacognosy, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India
[3]Department of Pharmaceuticals, Faculty of Pharmacy, Tishk International University, Erbil, Kurdistan Region, Iraq
Correspondence: Dr. Mohd. Javed Naim, Assistant professor, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Tishk International University, Erbil, Kurdistan Region, Iraq
Email: mohammad.javed@tiu.edu.iq

Doi: 10.23918/eajse.v8i3p251

Abstract: Curcumin is a fat-soluble natural substance obtained from *Curcuma longa* and finds its applications in treatment of numerous disorders and diseases. Apart from its vast pharmacological profile, it is also used as a flavoring agent in the Asian subcontinent. This has drawn attention of the scientists to use it as an important scaffold to prepare its synthetic derivatives in order to improve the efficacy as well as potency of drug molecules and also reducing their toxicity effects. Here we tried to give some deeper insights of curcumin with a focus on its biological activities and various synthetic derivatives with a view to get potential lead molecules for future drug discovery and expansion of its medicinal profile.

Keywords: Curcumin, Curcuma Longa, Anticancer, Antibacterial, Antioxidant

1. Introduction

Curcumin is an important polyphenol/herbal phytochemical extract belonging to Zingiberaceae family. It was first isolated in the year 1870 from dried ground rhizome of an Indian plant turmeric (*Curcuma longa* L.) and is very common in the Asian subcontinent as a natural coloring agent and food additive (Zielinska et al., 2020). The curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) which is also known as diferuloylmethane was first elucidated in 1910. As per WHO, the maximum permissible dose of curcumin is 0-1mg/kg body weight and is found to be well tolerated and safe even at higher doses (Hemalswarya et al., 2006; Sa and Das, 2008; WHO, 2000). Apart from curcumin, the other important curcuminoids includes demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin (Figure 1) (Kanubaddi et al., 2018). Curcumin also shares a vast pharmacological profile which includes anticancer, anti-inflammatory, anti-alzheimer, anti-oxidant, anti-bacterial, anti-tubercular, antidiabetic, antifungal, anti-SARS-CoV-2 etc. (Figure 2) (Kaur et al., 2016; Roxo et al., 2019). Curcumin is also found to target signaling molecules and activity at cellular level is responsible for its multiple health benefits (Gupta et al., 2016). Apart from its countless potential, majority of its beneficial effects are due to anti-oxidant and anti-inflammatory properties (Aggarwal et al., 2009). Inspite of having enormous activity potential, curcumin always suffer with poor absorption, poor bioavailability, rapid metabolism & elimination. As a result, newer approaches are being introduced in order to overcome these limitations so that we can improve the potency as well as the efficacy of curcumin.

Received: June 1, 2022
Accepted: December 1, 2022
Naim, J.N., & Ahamad, A., & Anwer, E.T., & Salahuddin, A.S. (2022). Curcumin: A Mini Review on its Synthetic Derivatives. *Eurasian Journal of Science and Engineering, 8*(3), 251-262.

Piperine which is obtained from black pepper as an active constituent is an important bioavailability enhancer which is associated with the enhancement of bioavailability of curcumin by 2000% (Han, 2011; Shoba et al., 1998). The sole purpose of this review is to impart an immediate overview of the research done on the synthesis of newer curcumin derivatives in this decade along with some important biological activities that have been discussed. The list of patents on various synthetic curcumin derivatives or complexes is highlighted in Table 1.

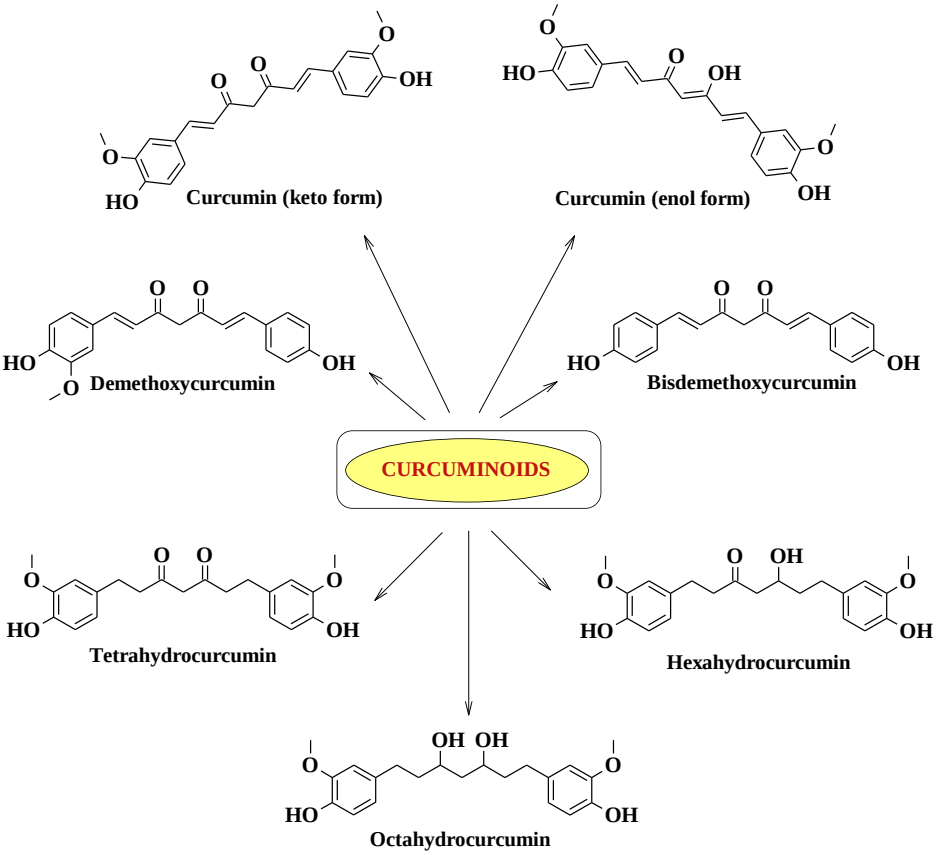


Figure 1: Structure of curcuminoids

Table 1: Patents on curcumin

S.No.	Patent no.	Patent date	Inventors	Description
1	US9724311B2 (Deshpande and Juturu, 2017)	08 Aug 2017	Jayant Deshpande, Vijaya Juturu	Curcumin compositions and uses thereof
2	WO2011106691A2 (Raja et al., 2011)	01 Sep 2011	Krishnaswami Raja, Alejandra Alonso, Probal Banerjee, Sukanta Dolai, Christopher Corbo, Saadyah Averick, Amit Mogha, Shawon Debnath	Curcumin derivatives
3	US8841326B2 (Jagt et al., 2014)	23 Sep 2014	David L. Vander Jagt, Lorraine M Deck, Steve F. Abcouwer, Robert A. Orlando, Robert E. Royer, Waylon M. Weber,	Therapeutic curcumin derivatives

			Ekaterina V. Bobrovnikova-Marjon, Lucy A. Hunsaker.	
4	US7507864B2 (Miller and Mitchell, 2009)	24 March 2009	Jeffrey Christopher Miller, Miguel O. Mitchell	Method for the synthesis of curcumin analogues
5	US5679864A (Krackov and Bellis, 1997)	21 Oct 1997	Mark Harry Krackov, Harold Edward Bellis	Process for the synthesis of curcumin-related compounds
6	US3479345A (Geschickter and Meadow, 1969)	18 Nov 1969	Charles F Geschickter, Jacob R Meadow	Curcumin derivatives

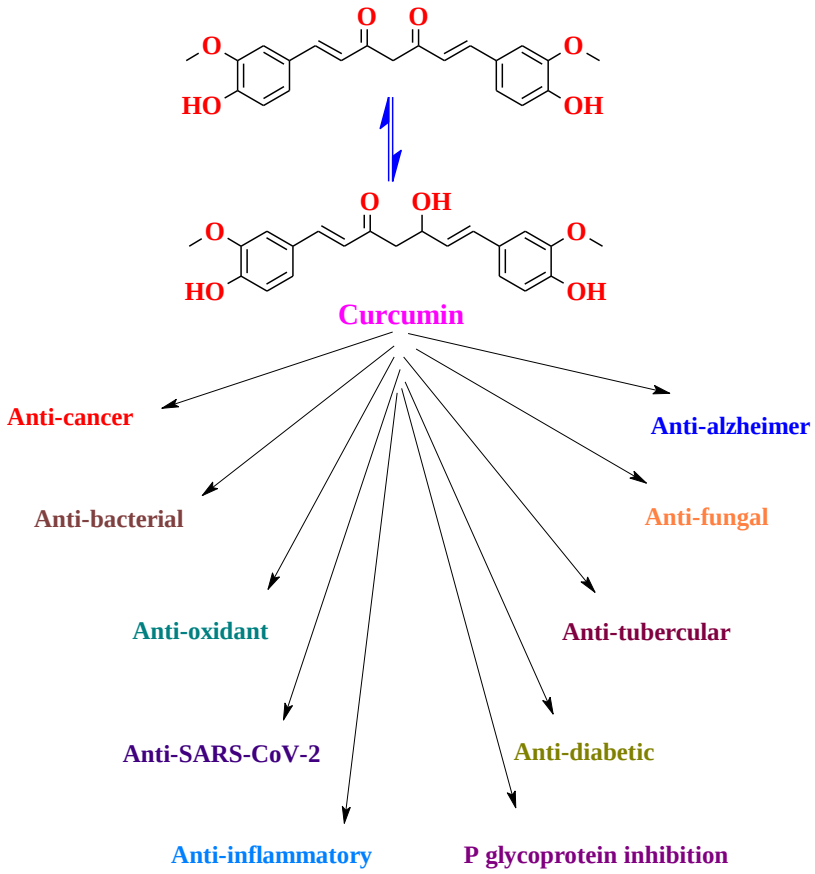


Figure 2: Pharmacological profile of curcumin along with its interconvertible keto-enol form

2. Pharmacological Profile of Curcumin

2.1 Anticancer Activity

Koroth et al. (2022) reported a curcumin derivative (1) 1,2-bis[(3E,5E)-3,5-bis[(2-chlorophenyl) methylene]-4-oxo-1-piperidyl] ethane-1,2-dione that exhibits almost 14 folds' better activity than curcumin and is found to be detectable in plasma for a period of 12 hours. It induces ROS, activates

intrinsic apoptotic pathway and proapoptotic proteins induction in PA1 and A2780 (ovarian cancer cell lines). It also found to block ovarian cancer cells migration. By activating intrinsic apoptotic pathway in vivo, it exerted its antitumor effect in EAC mouse model. Due to its enhanced bioavailability and stability that its parent compound curcumin, even its low doses are found to be effective against tumor progression with no superficial signs of systemic toxicity. Halevas et al. (2021) designed and synthesized a novel Ga(III)-curcumin complex with 1,10-phenanthroline (2) as photosensitizer in non-invasive photodynamic therapy for the treatment of cancer. This complex 2 was found to be more effective than normal curcumin in photostability, increased absorption maximum and comparable free radical generation and exhibited no dark toxicity at lower concentrations against breast cancer cell lines (MCF-7) and a light dose dependent reduction in survival of cell was observed upon irradiation. Pettinari et al. (2021) synthesized two cationic ruthenium (II) 1,4,7-trithiacyclononane ([9] aneS3) complexes of curcumin and bisdemethoxycurcumin using the precursor [RuCl2(dmso-S) ([9]-aneS3)]. The two synthesized complexes [Ru(curc)(dmso-S)([9]aneS3)]Cl (3) (IC50= >500μM, 165.9 ± 7.8μM and 116.1 ± 18.2μM) and [Ru(bdcurc)(dmso-S)([9]aneS3)]Cl (4) (IC50=>500μM, 233.7 ± 41.0μM and 191.3 ± 11.1μM) were then evaluated for anticancer potential using curcumin (IC50= 32.7 ± 5.0μM, 10.5 ± 0.4μM and 7.1 ± 3.2μM) and bisdemethoxycurcumin (IC50= 21.6 ± 9.8μM, 8.4 ± 3.3μM and 11.5 ± 1.8μM) as the reference against A549, MCF-7 and HCT116 cancer cell lines; where they displayed modest cytotoxic potential. Romanucci et al. (2021) carried out the solid phase synthesis of curcumin mimics without altering the seven nuclei distance between two phenylethanoid moieties and assessed them for anticancer potential against PANC1, PC3 and SW480 cancer cell lines. Compound 5 appeared as the most potential derivative which not only effectively inhibited cancer cell growth but also caused strong cell death. Zhang et al. (2019) have synthesized a novel series of curcumin peptide conjugates as PepT1-mediated transport drugs and evaluated them as antitumor agents against HepG2 and SMMC-7721 cell lines using MTT assay. Compound 6 showed most potential results with an IC50 values of 23.4 μM and 19.7 μM in comparison to curcumin which showed IC50 values of 35.8 μM and 22.9 μM against HepG2 and SMMC-7721 cell lines. Tu et al. (2017) have synthesized a series of curcumin analogs by introducing a geminal dimethyl group on the active methylene group and assessed them as Nrf2 activators (Nuclear factor erythroid-2-related factor 2) and for cytoprotection against oxidative death. Compound 7 appeared as the most potential lead in stability and cytoprotection through expression of phase II detoxifying enzymes in the Micahel acceptor and catechol dependent manner. Ruan et al. (2012) have synthesized curcumin based resveratrol derivatives and assessed for antiproliferative potential against B16-F10, HePG2 and A549 cancer cell lines. Compound 8 appeared most potent with an IC50 values of 0.71 ± 0.11 μg/ml (B16-F10), 1.60 ± 0.12 μg/ml (HePG2) and 2.10 ± 0.53 μg/ml (A549). It also exhibited significant tubulin polymerization inhibition of 1.45 ± 0.22 μg/ml. Ferrari et al. (2009) prepared curcumin derivatives by glycosylation of the aromatic ring of curcumin. The derivative not only showed improved kinetic stability and water solubility; but also retained their ability to coordinate metal ion particularly Ga(III) through β-diketo moiety. Compound 6 (IC50=9.8 ± 0.8μM and 40 ± 3.7μM) and 10 (IC50=22 ± 1.9μM and 83 ± 7 μM) displayed significant cytotoxicity against 2008 cell lines (serous cyst-adenocarcinoma of ovary) and C13* cell lines (cDDP resistant subline). Also compound 10 was found to be more selective and less toxic against non-tumorigenic cells (Figure 3).

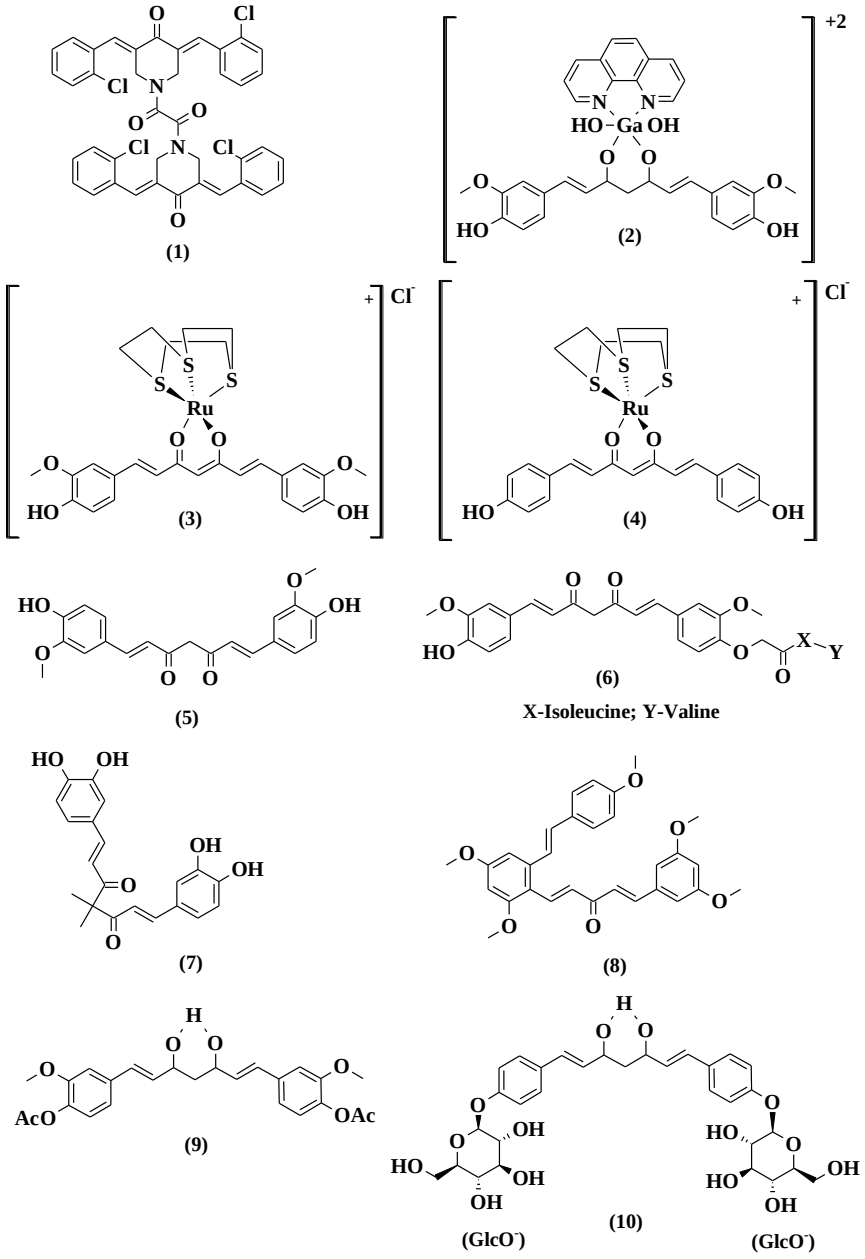


Figure 3: Synthetic curcumin derivatives as anticancer agents

2.2 Anti-alzheimer Activity

Park et al. (2021) have synthesized near infrared fluorescent probes based on curcumin pharmacophore to accurately diagnose and monitor the progression of Alzheimer diseases as well as determining the efficiency of medications in treating or managing it. Their sole purpose is to identify abnormal amyloid-β-plaques assembly into oligomers and insoluble fibrils. Compound 11 with an emission wavelength of 667 nm was found to be the most effective probe in clear visualization of plaques after 10 min of its administration. Elmegeed et al. (2015) have synthesized some novel steroidal curcumin derivatives and assessed them for anti-alzheimer activity. Compound 12 appeared as the most potential derivative and was found to enhance the levels of AcH, GSH, Paraoxenase and BCL2 lymphoma levels in treated patients (Figure 4).

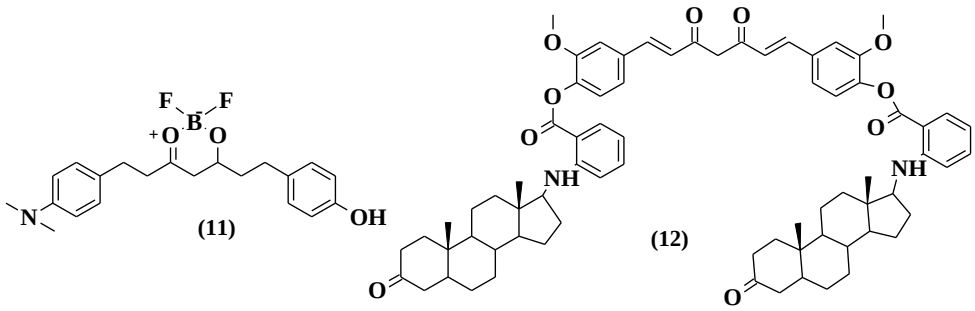


Figure 4: Synthetic curcumin derivatives as anti-alzheimer agents

2.3 Anti-diabetic Activity

Mehrabi et al. (2021) have synthesized curcumin based pyrano[2,3-d] pyrimidine derivatives by multicomponent reaction and evaluated them for inhibition of α-glucosidase & α-amylase and antioxidant activity. Compound 13 displayed highest possible inhibition of α-glucosidase & α-amylase whereas compound 14 displayed most potent antioxidant activity. Tavaf et al. (2020) have synthesized novel 4H-pyran heterocycles based on curcumin through multicomponent reaction involving curcumin, aldehydes and malonitrile and assessed them for inhibition of α-glucosidase & α-amylase and antioxidant activity. The compound 15 showed significant α-glucosidase inhibition with an IC50 value of 15.18 ± 0.65μM whereas 16 showed significant antioxidant activity 5.082 ± 0.031μM. The inhibition of α-amylase was found to be less than 20% in comparison to acarbose which showed more than 80% inhibition (Figure 5).

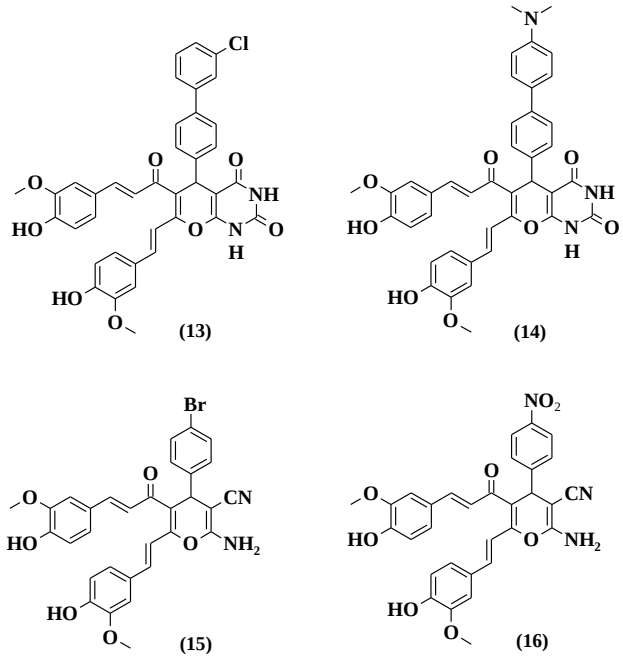
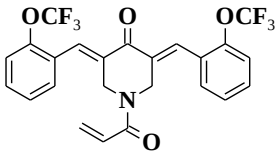


Figure 5: Synthetic curcumin derivatives as anti-diabetic agents

2.4 Anti-inflammatory Activity

Wang et al. (2021) have synthesized ortho substituted mono carbonyl derivatives of curcumin by replacing the β-diketone moiety of curcumin and assessed them for inflammatory potential. Compounds 17 displayed significant anti-inflammatory activity in lipopolysaccharide induced Raw264.7 macrophages and dextran sulfate sodium induced mouse model of colitis. On oral

administration; they decreased ulcerative colitis symptoms and reduced colonic tissues damage (Figure 6).

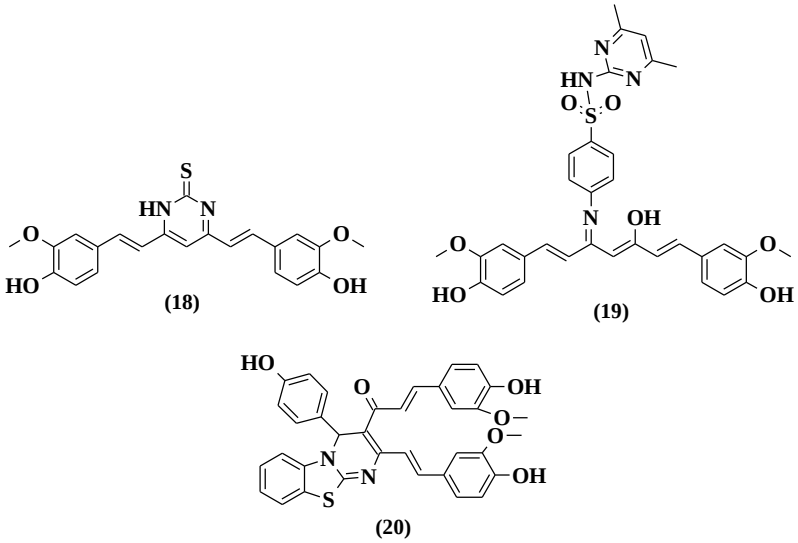


(17)

Figure 6: Synthetic curcumin derivatives as anti-diabetic agents

2.5 Anti-bacterial & Anti-fungal Activity

Shrivash et al. (2018) carried out the synthesis of novel curcumin derivatives by introducing the linker between two aromatic rings which was substituted with nitrogen and evaluated for antibacterial activity (Gram + and Gram -). Compound 18 was found to be the most potential derivative among the series that inhibited both gram+ and gram- bacteria to a greater extent. Lal et al. (2013) have carried out the synthesis of sulfonamide containing curcumin derivatives and evaluated them for antibacterial (S. aureus, B. cereus, S. Typhi, P. aeruginosa and E. coli), antifungal (A. niger, A. flavus, T. viride and C. lunata) and cytotoxic activity (Hela, HepG2, QG-56 and HCT116). Compound 19 showed most potent antibacterial and antifungal activity with MIC of 20μM (except A> flavus-MIC of > 80 μM) whereas the cytotoxicity (for 3e: IC50=25-50 μM) was even found to be more than curcumin (IC50=50-100 μM). Sahu et al. (2012) have synthesized a series of 4H-pyrimido[2,1-b] benzothiazole, pyrazole and benzylidene derivatives of curcumin through one pot synthesis procedures and assessed them for antibacterial (S. aureus, B. cereus, S. Typhi, P. aeruginosa, E. coli and P. rettgeri) and antifungal (A. niger, A. flavus and A. fumigatus) activities. Compound 20 appeared as the most active compound among the series (Figure 7).



(18) **(19)** **(20)**

Figure 7: Synthetic curcumin derivatives as anti-bacterial and anti-fungal agents

2.6 Anti-oxidant Activity

He et al. (2021) have synthesized novel monoenone monocarbonyl curcumin analogs using green synthesis employing edible proline as a catalyst; and possessed improved stability and reduced toxicity

in comparison to dienone monocarbonyl curcumin analogs that exhibited significant toxicity. These derivatives were assessed for antioxidant activity in which compound 21 was the most potential derivative. Hao et al. (2020) have synthesized come curcumin derivatives and assessed them for antioxidant potential. Compound 22 was found to be most potential which may be attributed to the presence isopentenyl group present on the aromatic rings. Călinescu et al. (2019) have synthesized copper (II) coordination compounds using curcumin, 2-hydrazinobenzothiazole and metal salts (1:2:1 & 1:2:2 ratio) through template synthesis and evaluated them for antioxidant activity by photochemiluminescence. Complex 23 showed highest antioxidant activity with 28.7% total antioxidant capacity in comparison to curcumin which showed only 17.07% (Figure 8).

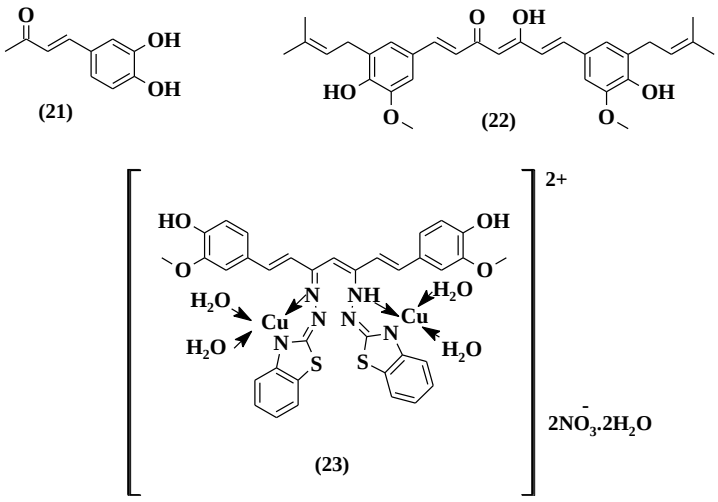


Figure 8: Synthetic curcumin derivatives as anti-oxidant agents

2.7 Anti-tubercular Activity

Subhedar et al. (2020) employed one pot multicomponent reaction for the synthesis of 3,5-bis (arylidene)-4-piperidones and assessed them for anti-tubercular activity against MTB H37Ra and M. Bovis BCG strains. Compound 24 showed maximum anti-tubercular potential with an IC50 value of 1.89 µg/ml against MTB H37Ra and 2.69 µg/ml against M. Bovis. In molecular docking studies, 4f showed hydrogen bonding interactions with Ile194 and π-π stacking hydrophobic interactions with Tyr158 and Trp222 (Figure 9).

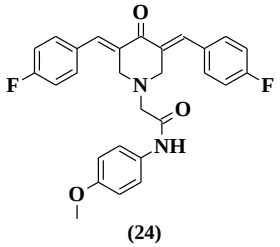
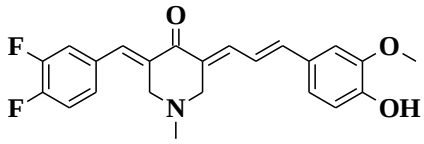


Figure 9: Synthetic curcumin derivatives as anti-tubercular agents

2.8 Anti- SARS-CoV-2 Activity

Alici et al. (2022) designed and carried out in silico studies of curcumin derivatives against 3CLPro, PLpro, NSP7/8/12, NSP7/8/12 +RNA, NSP15, NSP16, Spike, Spike+ACE enzymes (SARS-CoV-2

receptors) and evaluated them against enzymes associated with COVID-19. Compound 25 was found to be the most potential derivative with a docking core of -9.6 kcal/mol (Figure 10).

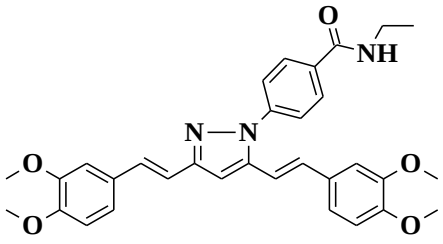


(25)

Figure 10: Synthetic curcumin derivatives as anti-SARS-CoV-2 agents

2.9 P-glycoprotein Inhibitors

Sagnou et al. (2020) have synthesized some pyrazole curcumin derivatives and assessed them as Pgp inhibitors. Compound 26 appeared as the most potential inhibitor in comparison to verapamil as standard drug. It was found to be less cytotoxic and the sensitivity to MDR of doxorubicin was re-established at sub-micromolar concentration (Figure 11).



(26)

Figure 11: Synthetic curcumin derivatives as P glycoprotein inhibitors

3. Conclusion

Curcumin has the required medicinal health benefits with multiple therapeutic effects on biochemical and physiological processes. The review revealed curcumin as an important pharmaceutical scaffold for the synthesis of various synthetic analogues/derivatives in order to expand its pharmacological profile and to increase its efficacy and potency by overcoming its various limitations that acts as a hurdle in its absorption and bioavailability.

References

Aggarwal, B.B. and Harikumar, K.B. (2009). Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *The international journal of biochemistry & cell biology*, *41*(1), 40-59.

Alici, H., Tahtaci, H. and Demir, K. (2022). Design and various in silico studies of the novel curcumin derivatives as potential candidates against COVID-19-associated main enzymes. *Computational biology and chemistry*, *98*, 107657.

Călinescu, M., Fiastru, M., Bala, D., Mihailciuc, C., Negreanu-Pîrjol, T. and Jurcă, B. (2019). Synthesis, characterization, electrochemical behavior and antioxidant activity of new copper (II) coordination compounds with curcumin derivatives. *Journal of Saudi Chemical Society*, *23*(7), 817-827.

Deshpande, J., and Juturu, V. (2017). Curcumin compositions and uses thereof. US9724311B2.

Elmegeed, G.A., Ahmed, H.H., Hashash, M.A., Abd-Elhalim, M.M. and El-Kady, D.S. (2015). Synthesis of novel steroidal curcumin derivatives as anti-Alzheimer's disease candidates: Evidences-based on in vivo study. *Steroids*, *101*, 78-89.

Ferrari, E., Lazzari, S., Marverti, G., Pignedoli, F., Spagnolo, F. and Saladini, M. (2009). Synthesis, cytotoxic and combined cDDP activity of new stable curcumin derivatives. *Bioorganic & medicinal chemistry*, *17*(8), 3043-3052.

Geschickter, C.F., Meadow, J.R. (1969). Curcumin derivatives. US3479345A.

Gupta, S.C., Patchva, S. and Aggarwal, B.B. (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. *The AAPS journal*, *15*(1), 195-218.

Halevas, E., Arvanitidou, M., Mavroidi, B., Hatzidimitriou, A.G., Politopoulos, K., Alexandratou, E., Pelecanou, M. and Sagnou, M. (2021). A novel curcumin gallium complex as photosensitizer in photodynamic therapy: Synthesis, structural and physicochemical characterization, photophysical properties and in vitro studies against breast cancer cells. *Journal of Molecular Structure*, *1240*, 130485.

Han, H.K. (2011). The effects of black pepper on the intestinal absorption and hepatic metabolism of drugs. *Expert opinion on drug metabolism & toxicology*, *7*(6), 721-729.

Hao, T., Wang, K., Zhang, S., Yang, S., Wang, P., Gao, F., Zhao, Y., Guo, N. and Yu, P. (2020). Preparation, characterization, antioxidant evaluation of new curcumin derivatives and effects of forming HSA-bound nanoparticles on the stability and activity. *European Journal of Medicinal Chemistry*, *207*, 112798.

He, W., Wang, J., Jin, Q., Zhang, J., Liu, Y., Jin, Z., Wang, H., Hu, L., Zhu, L., Shen, M. and Huang, L. (2021). Design, green synthesis, antioxidant activity screening, and evaluation of protective effect on cerebral ischemia reperfusion injury of novel monoenone monocarbonyl curcumin analogs. *Bioorganic Chemistry*, *114*, 105080.

HemaIswarya, S. and Doble, M. (2006). Potential synergism of natural products in the treatment of cancer. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *20*(4), 239-249.

Jagt, D.L.V., Deck, L.M., Abcouwer, S.F., Orlando, R.A., Royer, R.E., Weber, W.M., Bobrovnikova-Marjon, E.V., Hunsaker, L.A. (2014). Therapeutic curcumin derivatives US8841326B2.

Kanubaddi, K.R., Yang, S.H., Wu, L.W., Lee, C.H. and Weng, C.F. (2018). Nanoparticle-conjugated nutraceuticals exert prospectively palliative of amyloid aggregation. *International Journal of Nanomedicine*, *13*, 8473.

Kaur, G., Invally, M. and Chintamaneni, M. (2016). Influence of piperine and quercetin on antidiabetic potential of curcumin. *Journal of Complementary and Integrative Medicine*, *13*(3), 247-255.

Koroth, J., Mahadeva, R., Ravindran, F., Parashar, T.R., Teja, V., Karki, S.S. and Choudhary, B. (2022). Curcumin derivative 1, 2-bis [(3E, 5E)-3, 5-bis [(2-chlorophenyl) methylene]-4-oxo-1-piperidyl] ethane-1, 2-dione (ST03) induces mitochondria mediated apoptosis in ovarian cancer cells and inhibits tumor progression in EAC mouse model. *Translational oncology*, *15*(1), 101280.

Krackov, M.H., Bellis, H.E. (1997). Process for the synthesis of curcumin-related compounds. US5679864A.

Lal, J., Gupta, S.K., Thavaselvam, D. and Agarwal, D.D. (2013). Biological activity, design, synthesis and structure activity relationship of some novel derivatives of curcumin containing sulfonamides. *European Journal of Medicinal Chemistry*, *64*, 579-588.

Mehrabi, M., Esmaeili, S., Ezati, M., Abassi, M., Rasouli, H., Nazari, D., Adibi, H. and Khodarahmi, R. (2021). Antioxidant and glycohydrolase inhibitory behavior of curcumin-based compounds: Synthesis and evaluation of anti-diabetic properties in vitro. *Bioorganic chemistry*, *110*, 104720.

Miller, J.C., Mitchell, M.O. (2009). Method for the synthesis of curcumin analogues. US7507864B2

Park, Y.D., Kinger, M., Min, C., Lee, S.Y., Byun, Y., Park, J.W. and Jeon, J. (2021). Synthesis and evaluation of curcumin-based near-infrared fluorescent probes for the in vivo optical imaging of amyloid-β plaques. *Bioorganic Chemistry*, *115*, 05167.

Pettinari, R., Marchetti, F., Tombesi, A., Duan, F., Zhou, L., Messori, L., Giacomelli, C., Marchetti, L., Trincavelli, M.L., Marzo, T. and La Mendola, D. (2021). Ruthenium (II) 1, 4, 7-trithiacyclononane complexes of curcumin and bisdemethoxycurcumin: Synthesis, characterization, and biological activity. *Journal of Inorganic Biochemistry*, *218*, 111387.

Raja, K., Alonso, A., Banerjee, P., Dolai, S., Corbo, C., Averick, S., Mogha, A., Debnath, S. (2011). Curcumin derivatives. WO2011106691A2.

Romanucci, V., Giordano, M., Pagano, R., Agarwal, C., Agarwal, R., Zarrelli, A. and Di Fabio, G. (2021). Solid-phase synthesis of curcumin mimics and their anticancer activity against human pancreatic, prostate, and colorectal cancer cell lines. *Bioorganic & Medicinal Chemistry*, *42*, 116249.

Roxo, D.F., Arcaro, C.A., Gutierres, V.O., Costa, M.C., Oliveira, J.O., Lima, T.F.O., Assis, R.P., Brunetti, I.L. and Baviera, A.M. (2019). Curcumin combined with metformin decreases glycemia and dyslipidemia, and increases paraoxonase activity in diabetic rats. *Diabetology & metabolic syndrome*, *11*(1), 1-8.

Ruan, B.F., Lu, X., Li, T.T., Tang, J.F., Wei, Y., Wang, X.L., Zheng, S.L., Yao, R.S. and Zhu, H.L. (2012). Synthesis, biological evaluation and molecular docking studies of resveratrol derivatives possessing curcumin moiety as potent antitubulin agents. *Bioorganic & medicinal chemistry*, *20*(2), 1113-1121.

Sa, G. and Das, T., (2008). Anti-cancer effects of curcumin: cycle of life and death. *Cell division*, *3*(1), 1-14.

Sagnou, M., Novikov, F.N., Ivanova, E.S., Alexiou, P., Stroylov, V.S., Titov, I.Y., Tatarskiy, V.V., Vagida, M.S., Pelecanou, M., Shtil, A.A. and Chilov, G.G. (2020). Novel curcumin derivatives as P-glycoprotein inhibitors: Molecular modeling, synthesis and sensitization of multidrug resistant cells to doxorubicin. *European Journal of Medicinal Chemistry*, *198*, 112331.

Sahu, P.K., Sahu, P.K., Gupta, S.K., Thavaselvam, D. and Agarwal, D.D. (2012). Synthesis and evaluation of antimicrobial activity of 4H-pyrimido [2, 1-b] benzothiazole, pyrazole and benzylidene derivatives of curcumin. *European journal of medicinal chemistry*, *54*, 366-378.

Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R. and Srinivas, P.S.S.R. (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta medica*, *64*(04), 353-356.

Shrivash, M.K., Mishra, S., Pandey, J. and Misra, K. (2018). In-silico designing, chemical synthesis, characterization and in-vitro assessment of antibacterial properties of some analogues of curcumin. *Microbial pathogenesis*, *123*, 89-97.

Subhedar, D.D., Shaikh, M.H., Nagargoje, A.A., Akolkar, S.V., Bhansali, S.G., Sarkar, D. and Shingate, B.B. (2020). Amide-linked monocarbonyl curcumin analogues: efficient

synthesis, antitubercular activity and molecular docking study. *Polycyclic Aromatic Compounds*, 1-17.

Tavaf, Z., Dangolani, S.K., Yousefi, R., Panahi, F., Shahsavani, M.B. and Khalafi-Nezhad, A. (2020). Synthesis of new curcumin derivatives as influential antidiabetic α-glucosidase and α-amylase inhibitors with anti-oxidant activity. *Carbohydrate Research*, *494*, 108069.

Tu, Z.S., Wang, Q., Sun, D.D., Dai, F. and Zhou, B. (2017). Design, synthesis, and evaluation of curcumin derivatives as Nrf2 activators and cytoprotectors against oxidative death. *European journal of medicinal chemistry*, *134*, 72-85.

Wang, Z., Mu, W., Li, P., Liu, G. and Yang, J. (2021). Anti-inflammatory activity of ortho-trifluoromethoxy-substituted 4-piperidione-containing mono-carbonyl curcumin derivatives in vitro and in vivo. *European Journal of Pharmaceutical Sciences*, *160*, 105756.

WHO. (2000). Evaluation of Certain Food Additives. WHO Technical Report Series, vol. 891 WHO, Geneva.

Zhang, J., Wen, H., Shen, F., Wang, X., Shan, C., Chai, C., Liu, J. and Li, W. (2019). Synthesis and biological evaluation of a novel series of curcumin-peptide derivatives as PepT1-mediated transport drugs. *Bioorganic Chemistry*, *92*, 103163.

Zielińska, A., Alves, H., Marques, V., Durazzo, A., Lucarini, M., Alves, T.F., Morsink, M., Willemen, N., Eder, P., Chaud, M.V. and Severino, P. (2020). Properties, extraction methods, and delivery systems for curcumin as a natural source of beneficial health effects. *Medicina*, *56*(7), 336.