Asian Jr. of Microbiol. Biotech. Env. Sc. Vol. 23, No. (3) : 2021 : 328-334

ISSN-0972-3005

THERAPEUTIC EFFECT OF CURCUMIN DERIVATIVES/ANALOGUES OF INDIAN SPICE TURMERIC

ANJALI[1]*, UDAYA PRATAP SINGH[2], RUBINA LAWRENCE[1] AND EBENEZER JEYAKUMAR[1]

[1]Department of Industrial Microbiology
Jacob Institute of Biotechnology and Bioengineering,
Sam Higginbottom University of Agriculture, Technology and Sciences,
Prayagraj, Uttar Pradesh, India
[2]Department of Pharmaceutical Science
Shalom Institute of Health and Allied Sciences
Sam Higginbottom University of Agriculture, Technology and Sciences,
Prayagraj, Uttar Pradesh, India

(Received 21 April, 2021; Accepted 7 May, 2021)

***Key words**: Curcumin, Analogues, Biological activities, Pharmacological activities, Physicochemical features*

Abstract - Curcumin (CU), an edible natural pigment from the rhizome of *Curcuma longa*, (Turmeric) has demonstrated extensive anti-oxidant, anti-inflammatory, anti-microbial, anti-diabetic and anti-cancer activity in vivo and in vitro. With the physicochemical features of reversing low solubility, less bio accessibility and poor stability, CU structure has to be modified chemically through substituting functional ailments or to develop the CU hybrids. However, the poor stability, solubility, in vivo bioavailability and weak activity of CU greatly limit its therapeutic applications. Therefore, modified CU analogues have been extensively studied to determine the variety of biological and pharmacological activities, providing protection against infectious agents and chronic diseases. Starting from the study of natural CU analogues, multiple approaches are being sought to obtain more stable, soluble and effective analogues of CU. This review also displayed the bioactivity of Curcumin and its analogues in combination of with other biologically active compounds and describe the most recent and potent analogues againstthe infectious agents and chronic disorders.

INTRODUCTION

Many natural economic products have been isolated and characterized for the welfare of human society (Che *et al*., 2019). These natural products have medicinal property to tackle a wide range of human diseases that affects the human health (Hewlings and Kalman, 2017). Curcumin is one of the extensively studied natural edible pigment or chemically, called as diferuloylmethane, a major phytochemical derivative obtained from the perennial herbal plant named as *Curcuma longa* (Zingiberaceae family) (Chanda and Ramachandra, 2019), its common name is turmeric or well known as golden spice. Additionally, other secondary metabolites like Bisdemethoxycurcumin, and Demethoxycurcumin, Sesquiterpenes, and Steroids (Omosa *et al*., 2017); were also isolated from the rhizome of traditional herbal plant.

Actually, Curcumin is one of the main polyphenolic compounds of turmeric (*Curcuma longa* L.) that imparts a unique yellowish color to the herb. Turmeric is extensively cultivated in India and South East Asia with having a broad spectrum of pharmacological activities against the various infectious agents (Praditya *et al.* 2019). Despite of this, Curcumin is an active ingredient of turmeric chemically; it is a Bis-α, β-unsaturated β-diketone (Fig. 1) which possess the property of two conjugated and interconvertible keto-enol tautomer's structure.

To date, literature search concerning with natural product as therapeutic agent is available at pubmed.gov finds over 11,000 publications but it still remains an area of research on clinical studies using Curcumin and its derivatives. In this review, the updated overview of biological activities of Curcumin derivatives and its analogues with a wide

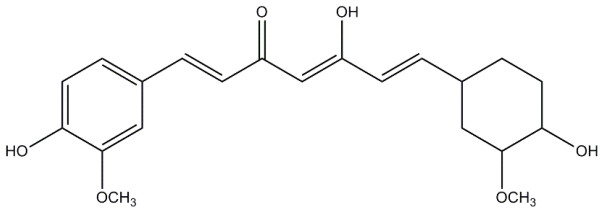
range of applications has been described and highlights the most potent analogues of Curcuminin a different section of biological studies.

CURCUMIN BIOACTIVITY STUDIES

Antioxidant activity

An endogenous oxidative damage occurs as a result of imbalance between the free radicals and antioxidants, (Zeeshan *et al*., 2016) and this imbalance causes a diverse array of chronic disorders (Tolahunase *et al*., 2017).

Earlier reports on Curcumin structure (He *et al*., 2017; Zhang and Tsai, 2016) revealed that electron donating group's presence, especially of phenolic hydroxyl groups in its chemical structure contributes its antioxidant activity against the reactive oxygen species (ROS) and maintained it in a balance state.



(1)

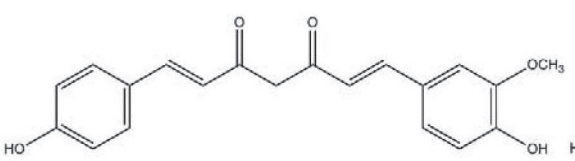
Fig. 1. Curcumin Chemical Structure

Alone Curcumin doesn't have enough ability to combat the harmful effect of serious diseases on healthier tissues thus, it cannot be approved as therapeutic agents evidently demonstrate it by clinical studies on animal models (Peng *et al*., 2018). The two typically studied Curcumin analogs are natural and another one is synthetic. Among the category of natural analog of turmeric, demethoxy analogs namely, Demethoxycurcumin (Dmc) (2) and Bisdemethoxycurcumin (Bdmc) (3), (Mishra and Gupta, 2020) are usually obtained with Curcumin in turmeric extracts. The Curcumin transformed metabolites are Curcumin glucuronide, Curcumin sulfate, Dihydrocurcumin (DHC) and Tetrahydrocurcumin (THC) (3), Hexahydrocurcumin (HHC) and Octahydrocurcumin (OHC) (Jude *et al*., 2018). However, to date, Tetrahydrocurcumin (THC) antioxidant activity was studied in vivo and in vitro in order to protect the cells from oxidative stress by scavenging the free radical species, lipid peroxidation and in the formation of Hydroperoxides. Still research on HHC and OHC derivatives of Curcumin is progressing to investigate the antioxidant activities have not been reported.

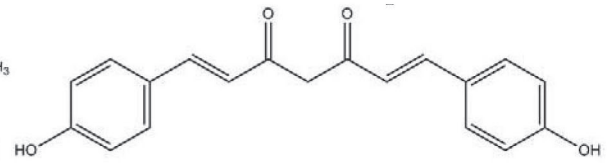
Anti-inflammatory activity

In general, when Individuals experienced an infection or injuries, their innate defense mechanism is activated and showed the sign of inflammation as an inflammatory response (Li *et al*., 2016). Curcumin anti-inflammatory activity suppresses the Prostaglandins (PGs) synthesis by inhibiting the cyclooxygenase (COX) enzyme activity, a key responsible enzyme for the conversion of Arachidonic acid to PGs which provokes the inflammatory responses (Ur-Rashid *et al*., 2019).

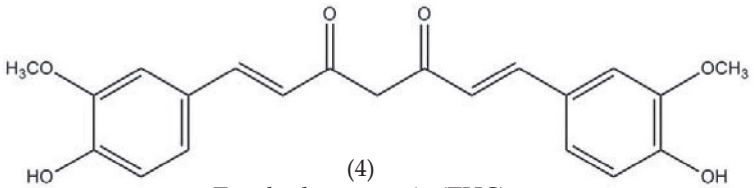
Actually, cyclooxygenase has two isoenzymes designated as COX-1 and COX-2 (Zhang *et al*., 2018a). Previous studies anticipated that COX-1 and



(2)
Demethoxycurcumin (Dmc)

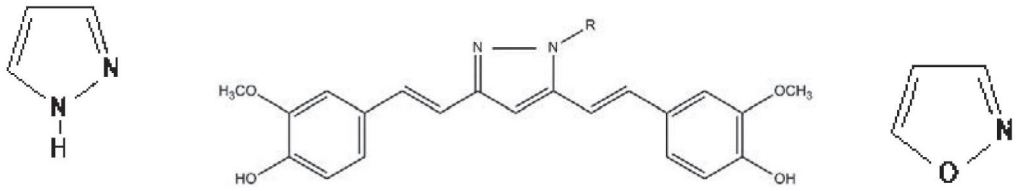


(3)
Bisdemethoxycurcumin (Bdmc)



(4)
Tetrahydrocurcumin (THC)

Fig 2. Antioxidant activity of Curcumin and its derivatives



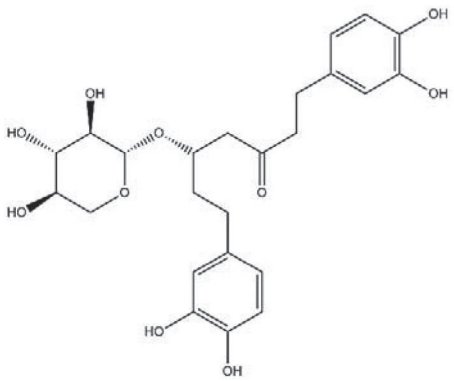
(5) (6) (7)

Fig. 3. Curcumin Pyrazole and its derivative and isoxazole

COX-2 dual inhibitors were more appropriate for treating chronic inflammation as observed in rheumatoid arthritis cases. However, many coworkers suggested to develop the Curcumin analog Tetrahydrocurcumin and Octahydrocurcumin and showed suppression of transforming growth factor â activated kinase-1 (TAK1) (Zhang *et al*., 2018) while the highest percent inhibition of PGs synthesis by inhibiting the activity of COX-2 (4). (Kumar *et al*., 2016) studied the novel pyrazole (5) derivatives (6) and isoxazole (7) analogs of Curcumin (Fig. 3) for their anti-inflammatory activity. In spite of this, other authors suggested that the pyrazole ring incorporation in place of â-diketone moiety of Curcumin has significantly enhances the COX-2/COX-1 activity to many folds and hence, the Curcumin anti-inflammatory activity have been improved (Zhang *et al*., 2018b).

Among the category of Curcumin natural analog, one of the recently modified Curcumin compound is oregonin, chemically it is [(5S)-1,7-bis(3,4-dihydroxyphenyl)-5-[(2S,3R,4S,5R)-3,4,5-trihydroxyoxan-2-yl]oxyheptan-3-one] (8) Fig 4. having a natural anti-inflammatory capacity (Arshad *et al*., 2017).

It was observed earlier that lipophilic and polar substituents on the phenyl ring of Curcumin such as



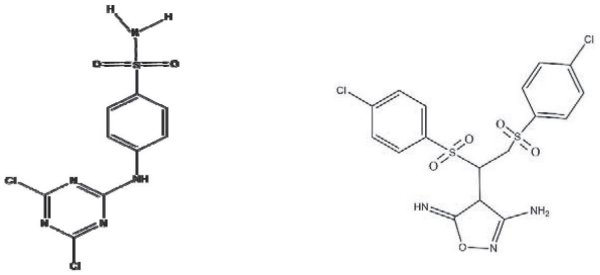
(8)

Fig. 4. Modified Curcumin compound with anti-inflammatory capacity

methoxy or methyl ester groups determines the specificity, subsequently, their substituent position evaluates the anti-inflammatory activity of a series of novel Curcumin analogues.

Antimicrobial activity

Curcumin (CU) is known to display antimicrobial activity against the wide range of bacterial species. Gram positive bacteria species are more sensitive to antimicrobial agents as compare to gram negative bacteria species (Srivastava *et al*., 2019). This resistive nature of gram-negative bacteria towards the antimicrobial agents is because of the presence of Lipopolysaccharides (LPS) components are involved to makeup outer envelope of the cell wall (Guest and Raivio, 2016). Recent research has shown evidence that methicillin-resistive *Staphylococcus aureus* (MRSA) spreading is difficult to control especially in under developed countries. However, Curcumin and its derivatives has a remarkable tendency to suppresses the growth of methicillin-resistive *Staphylococcus aureus* as well as other pathogenic bacteria such as *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhimurium*, *Stenotrophomonas maltophilia*, (Betts *et al*., 2016) *Streptococcusmutans* (Li *et al*., 2019) and *Klebsiella pneumoniae* (Alikiaii *et al*., 2020) etc. but its low solubility exception limits the sensitivity of gram negative bacteria. Groups substitutions in (CA) greatly enhanced potency of antibacterial activity than Curcumin against the number of bacterial strains including *Pseudomonas aeruginosa*, *Escherichia coli* (9), *Klebsiella pneumonia*, *Bacillus subtilis* and *Proteus vulgaris* (10) (Tariq *et al*., 2019) etc. A progression of a new class of 1,3,5-triazine bearing benzenesulfonamides (4-[(4,6-dichloro-1,3,5-triazin-2-yl)amino] benzenesulfonamide) (9) and [1-amide (3-oxale-5-yl benzene disulfonamide) 1,4 di chloride] (10), Fig. 5 is prepared and screened out of in vitro antibacterial activity by some scientists All these newly developed CU hybrids were showed moderate to promising antibacterial activity against

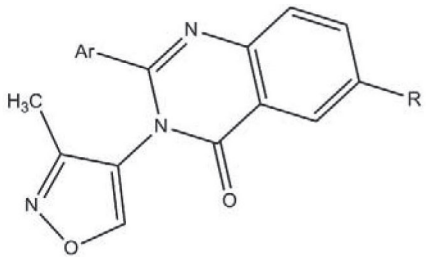


(9) (10)

Fig. 5. Antibacterial sulfonamide derivative

Pseudomonas aeruginosa and *Escherichia coli* bacterial strains as well as *Klebsiella pneumonia*, *B. subtilis* and *Proteus vulgaris*, with minimum inhibitory concentration (MIC) in the range of 25-250 μg/ml and 10 mg/ml (Rakesh *et al.*, 2017).

These Cu-hybrids possess the significant antimicrobial and anti-inflammatory activities and the highest cytotoxicity effect against the infectious agents. In addition, (Subhedar *et al*., 2020) developed the xanthene analogues namely 3, 5-bis (arylidene)-4-piperidones (11) Fig. 6 and evaluates the antitubercular activity of xanthene conjugates.



(11)

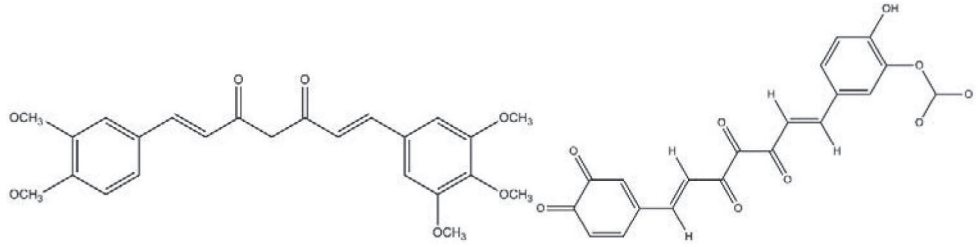
Fig. 6. Xanthine conjugates with anti-tubercular activity

Curcumin and its derivates had an inhibitory effect on fungal species like *Cryptococcus neoformans* and *Candida dubliniensis*. Hence, Curcumin act as a potential candidate for the treatment of candidiasis caused by candida species, including some fluconazole resistant strains and clinical isolates of *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida guilliermondii*, and *Candida krusei*. Photodynamic effect seriously affect the populations of *Candida albicans* in either planktonic or biofilm cultures probably through increasing the uptake of Curcumin (CU). Recent studies (Mustafa *et al*., 2018) explored the Curcumin derivatives namely, [1,7-Bis (3,4,5- trimethoxy phenyl)]-1,6-heptadiene-3,5-dione (12) and (4E)-2-[(E)-3-[3-(dimethoxymethoxy)-4-hydroxyphenyl] prop-2-enoyl]-5-(3-methyloxoniumylidene-4-oxocyclohexa-1,5-dien-1-yl)-3-oxopenta-1,4-dien-1-olate (Polaquini *et al.*, 2017) Fig. 7 displaying the antifungal activity against the Aspergillus, Penicillium and Alternaria genera of fungus.

Anticancer activity

Curcumin analogues namely, Thalidomide alone or in combination with other drugs is an effective treatment strategy against the malignant myeloma (MM) but, unfortunately, it may cause serious side effects (Alanazi *et al.*, 2019). However, to-date, pancreatic cancer is becoming a serious cause of death around the world. So many researchers stated that the difluorinated-curcumin (CDF), a Curcumin derivative was studied on pancreatic cell lines to demonstrate its activity against the cancerous cells (Momtazi and Shebkar, 2016). Recent research on colorectal cancer studied the two Curcumin derivative designated as EF31 and UB109 (Rajitha *et al.* 2016) showed that it exhibits a significant ability to suppress the growth of cancerous colorectal cell lines effectively through the inhibition of COX-2, STAT-3 and relevant transcriptional factor's (TFs).

In spite of this, two novel anti breast cancer Curcumin analogues namely, [3-(5-chlorofuran-2-yl)-5-methyl-4-phenylisoxazole] (14), 5-bis(4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidine (PAC)(15) and 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione(MAC) (16) (Fig. 8) a highly selective COX-1 inhibitor have been synthesized recently (Gao *et al*., 2020) and they



(12) (13)

Fig. 7. Antifungal curcumin derivatives

showed the five times higher efficiency capacity of inducing apoptosis in breast cancer cell lines. All the obtained results clearly indicate that Curcumin analogs have a higher potential to treat as therapeutic agent due to its inherent higher stability in blood, higher water solubility, greater bioavailability and bio-distribution than Curcumin (CU).

Anti-HIV activity

Several work describes the anti-viral properties of Curcumin (CU) refer to its efficacy against human immune-deficiency virus (HIV). Indeed, Curcumin and its derivatives had a great impact on HIV functioning and effects the different stages of the virus lifecycle (Praditya *et al.*, 2019). Alone Curcumin could reduce an inflammation in the female genital tract (FGT), which is known to facilitate HIV procurement. Despite of these advantages, Curcumin analogues can even inhibit the HIV replication by dysfunction the expression of several viral proteins including the viral integrase, protease as well as it retards the functioning of essential trans-activator of transcription (Tat) and gp120, important for the expression of HIV Proteins. Actually this review targeted HIV-1 transcription and replication with small molecules. Previously, published studies indicate that HIV-1 functioning can be retarded completely by targeting its protein phosphatase-1 and iron chelating compounds with using a novel Curcumin analog (Xionghao *et al.*, 2017) Curcumin-A (17) Fig. 9 (Gao *et al.*, 2019). These exciting results were significant in light of the current efforts to eradicate HIV-1 infection completely through permanent inhibition.

CONCLUSION

Curcumin (CU) and its ingredient originally have a great potential therapeutic effect against the infectious agents and used as herbal agent for the treatment of several risky disorders like Cancer and HIV. In spite of all these advantages, It has some restrictions like poor stability and solubility, and less

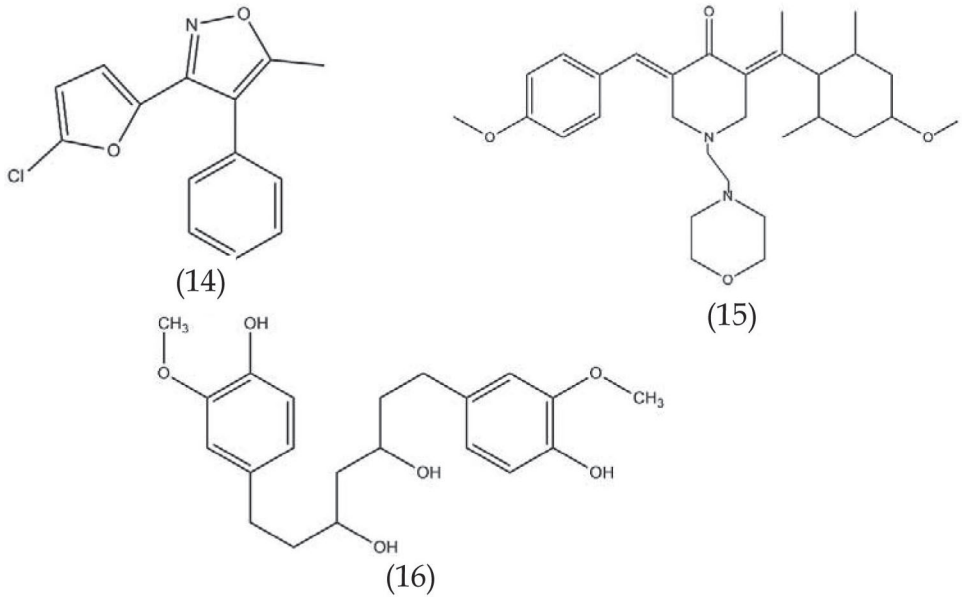


Fig. 8 Curcumin analogues with anticancer activities

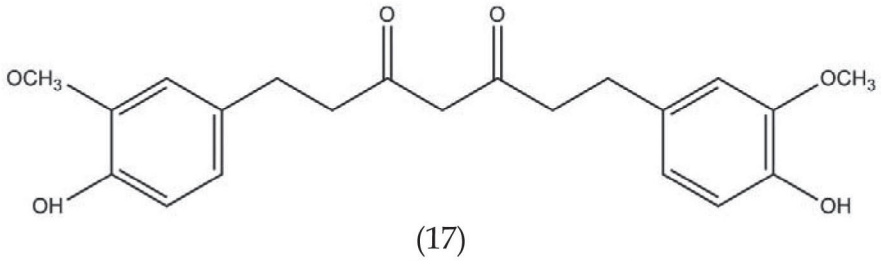


Fig. 9. Antiviral Curcumin analog

bioaccessibility which greatly limit its therapeutic applications. Therefore, potential bio active CU analogues have been extensively studied in order to develop a new natural therapeutic product of Curcumin synthetically with no side effect to overcome these limitations. In addition to curcumin, the turmeric extract also contains a Demethoxy analogues, Demethoxycurcumin (Dmc) and Bisdemethoxycurcumin (Bdmc) with having a natural tendency to fight against oxidative stress. However, the transformed Curcumin metabolites like Curcumin glucuronide, Curcumin sulfate, Dihydrocurcumin (DHC) and Tetrahydrocurcumin (THC) were also studied in animal model to reflect the best possible antioxidant activity. Recent studies revealed that modified Curcumin via through group substitutions or discover the potential synthetic derivatives in combination with Curcumin showed the more pronounced ant-inflammatory, antimicrobial and anticancer activity. As an anticancer agent, a new CU hybrid, the EF24 most recent one was developed and blocked the JAK-STAT-3 Pathway, COX-2 and telomerase activity to inhibit the cancerous cell proliferation as reported in cervical cancer. Indeed, Curcumin and its derivatives had anti-HIV activity down-regulate the Tight junction (TJ) proteins and restrict the entry of HIV-1 into epithelial cell lining of female genital tract by the blocking the expression of (Tat) and gp120 transcriptional factors. Thus, the several biological applications of Curcumin and its derivatives were elaborately discussed in this review article, and yet to be discover further for future studies.

REFERENCES

Akter, J., Hossain, M.A., Takara,K., Islam, M.Z. and Hou, D.X. 2018. Antioxidant activity of different species and varieties of turmeric (Curcuma spp): Isolation of active compounds. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*. 215 : 9-17.

Alanazi, F., Kwa, F.A.A., Burchall, G. and Jackson, D.E. 2019. New-generation drugs for treatment of multiple myeloma. *Drug Discovery Today*. 25 : 367-379.

Alikiaii, B., Bagherniya, M., Askari, G., Sathyapalan, T. and Sahebkar, A. 2020. Evaluation of the effect of curcumin on pneumonia: A systematic review of preclinical studies. *Phytotherapy Research.* 1–14.

Amalraj, A., Pius, A. and Gopi, S. 2016. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives a review. *Journal of Traditional Complement Medicine.* 7 : 205–233.

Amalraj, A., Pius, A. and Gopi, S. 2017. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives: A review. *Journal of Traditional Complement Medicines.* 7 : 205–233.

Amina, S., Yusuf, Sada, I., Hassan, Y., Temitope, O., Olomola, Adeyemi, C.M, Sunda, O. and Ajibade, 2018. Synthesis, antimalarial activity, and docking studies of monocarbonyl analogues of curcumin. *Ovidius University Annals of Chemistry*. 29 : 92-96.

Arshad, L., Haque, M.A., Bukhari, A.S.N. and Jantan, I. 2017. An overview of structure–activity relationship studies of curcumin analogs as antioxidant and anti-inflammatory agents. *Future Medicinal Chemistry.* 9 : 605–626.

Betts, J.W., Sharili, A.S., Ragione, L.R.M. and Wareham, D.W. 2016. *In vitro* antibacterial activity of curcumin-polymyxin B combinations against multidrug-resistant bacteria associated with traumatic wound infections. *Journal of Natural Product*. 79: 1702–1706.

Chanda, S. and Ramachandra, T.V. 2019. Phytochemical and Pharmacological Importance of Turmeric (Curcuma longa): A Review. *Research and Reviews: Asian Journal of Pharmacology*. 9 : 16-23.

Che, C.T. and Zhang, H. 2019. Plant Natural Products for Human Health. *International Journal of Molecular Sciences.* 20 : 830.

Gagliardi, S., Franco, V., Sorrentino, S., Zucca, S., Pandini, C., Rota, P., Bernuzzi, S., Costa, A., Sinforiani, E., Pansarasa, O., Cashman, J.R. and Cereda, C. 2018. Curcumin and Novel Synthetic Analogs in Cell-Based Studies of Alzheimer's Disease. *Frontiers in Pharmacology*. 9 : 1404.

Gao, L., Zhao, P., Li, Y., Yang, D., Hu, P., Li, L., Cheng, Y. and Yao, H. 2020. Reversal of PGlycoprotein-Mediated Multidrug Resistance by Novel Curcumin Analogues in Paclitaxel-resistant Human Breast Cancer Cells. *Biochemistry and Cell Biology*.

Gao, Y., Tai, W., Wang, N., Li, X., Jiang, S., Debnath, A.K., Du, L. and Chen, S. 2019. Identification of Novel Natural Products as Effective and Broad-Spectrum Anti-Zika Virus Inhibitors. *Viruses*. 11 : 1019.

Guest, R.L. and Raivio, T.L. 2016. Role of the Gram-Negative Envelope Stress Response in the Presence of Antimicrobial Agents. *Trends in Microbiology.* 24 : 377–390.

He, L., He, T., Farrar, S., Ji, L., Liu, T. and Ma, X. 2017. Antioxidants Maintain Cellular Redox Homeostasis by Elimination of Reactive Oxygen Species. *Cellular physiology and Biochemistry*. 44 : 1-22.

Hewlings, S.J.I.D., Kalman, D.S. 2017. Curcumin: A review of its effect on human health. *Foods*. 6 : 1-11.

Jude, S., Amalraj, A., Kunnumakkara, A., Divya, C., Loffler, B.M. and Gopi, S. 2018. Development of Validated Methods and Quantification of Curcuminoids and Curcumin Metabolites and Their Pharmacokinetic Study of Oral Administration of Complete Natural Turmeric Formulation (Cureit™) in Human Plasma via UPLC/ESI-Q-TOF-MS Spectrometry. *Molecules.*

23: 2415.

Kumar, S.R., Arif, I.A., Ahamed, A. and Idhayadhulla, A. 2016. Anti-inflammatory and antimicrobial activities of novel pyrazole analogues. *Saudi Journal of Biological Science*. 23 : 614–620.

Li, W., Suwanwela, N.C. and Patumraj, S. 2016. Curcumin by down-regulating NF-kB and elevating Nrf2, reduces brain edema and neurological dysfunction after cerebral I/R. *Microvascular Research*. 106 : 117–127.

Li, X., Yin, L., Ramage,G., Li,B., Tao,Y., Zhi, Q., Lin, H., Zhou, Y. 2016. Assessing the impact of curcumin on dual-species biofilms formed by *Streptococcus mutans* and *Candida albicans*. *Microbiology Open*. 8 : 937.

Li, X.J., Yang, Y.J., Li, Y. S., Zhang, W.K. and Tang, H.B. 2016. Alpha Pinene, linalool, and 1-octanol contribute to the topical anti-inflammatory and analgesic activities of frankincense by inhibiting COX-2. *Journal of Ethnopharmacology*. 179 : 22–26.

Mishra, R., Anil, K. and Gupta, A.K. 2020. Biological Activities of Curcuminoids: Chapter-8 The Chemistry and Bioactive Components of Turmeric RCS. *Food Chemistry, Function and Analysis.*

Momtazi, A.A. and Sahebkar, A. 2016. Difluorinated Curcumin: A Promising Curcumin Analogue with Improved Anti-Tumor Activity and Pharmacokinetic Profile. *Current Pharmaceutical Design.* 22 : 4386-97.

Mustafa, Y.F., Najem, M.A. and Tawffiq, Z.S. 2018. Coumarins from creston apple seeds: Isolation, chemical modification, and cytotoxicity study. *Journal of Applied Pharmaceutical Sciences.* 8 : 49–56.

Omosa, L.K., Midiwo, J.O. and Kuete, V. 2017. Curcuma longa," in Therapeutic Potential Against Metabolic, Inflammatory, *Infectious and Systemic Diseases*. Academic Press. 425–435.

Pappas, P.G., Kauffman, C.A., Andes, D., Clancy, C.J., Marr, K.A., Ostrosky-Zeichner, L., Reboli, A.C., Reboli, M.G., Vazquez, J.A., Walsh, T.J., Zaoutis, T.E. and Sobel, J.D. 2016. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clinical Infectious Disease.* 62 : 1-50.

Peng, S., Li, Z., Zou, L., Liu, W., Liu, C. and Clements, D.J.M. 2018. Enhancement of curcumin bioavailability by encapsulation in sophorolipid-coated nanoparticles: an in vitro and in vivo study. *Journal of Agriculture and Food Chemistry.* 66 : 1488-1497.

Praditya, D., Kirchhoff, L., Bruning, J., Rachmawati, H., Steinmann, J. and Steinmann, E. 2019. Anti-infective Properties of the Golden Spice Curcumin. *Frontiers in Microbiology.* 10 : 1-16.

Rajitha, B., Nagaraju, G.P., Shaib, W.L., Alese, O.B., Snyder, J.P., Shoji, M., Pattnaik, S., Alam, A. and El-Rayes, B.F. 2016. Novel synthetic curcumin analogs as potent antiangiogenic agents in colorectal cancer. *Molecular Carcinogenesis*. 56 : 288–299.

Rakesh, K.P., Shantharam, C.S., Sridhara, M.B., Manukumar, H.M. and Qin, H-L. 2017. Benzisoxazole: a privileged scaffold for medicinal chemistry. *Medicinal Chemistry Communications.* 8 : 2023–2039.

Srivastava, P., Shukla, M., Kaul, G., Chopra, S. and Patra, A.K. 2019. Rationally designed curcumin based ruthenium(II) antimicrobials effective against drug-resistant *Staphylococcus aureus*. *Dalton Transaction*. 48: 11822–11828.

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.

Tariq, S., Wani, S., Rasool, W., Bhat, M.A., Prabhakar, A., Shalla, A.H. and Rather, M.A. 2019. A comprehensive review of the antibacterial, antifungal and antiviral potential of essential oils and their chemical constituents against drug-resistant microbial pathogens. *Microbial Pathogenesis*. 134 : 1-20.

Tolahunase, O.M., Sagar, R. and Dada, R. 2017. Impact of Yoga and Meditation on Cellular Aging in Apparently Healthy Individuals: A Prospective, Open-Label Single-Arm Exploratory Study. *Oxidative Medicine and Cellular Longevity*. 9

Ur -Rashid, H., Yiming, X., Ahmad, N., Muhammad, Y. and Wang, L. 2019. Promising anti-inflammatory effects of chalcones via inhibition of cyclooxygenase, prostaglandin E2, inducible NO synthase and nuclear factor êB activities. *Bioorganic Chemistry*. 87 : 335-365.

Xionghao, L., Tatyana, A., Namita, K., Sergei, N. 2017. Protein Phosphatase-1 targeted Small Molecules, Iron Chelators and Curcumin Analogs as HIV-1 Antivirals. *Current Pharmaceutical Design*. 23 : 4122-4132.

Zeeshan ,H.M.A., Lee, G.H., Kim H-R and Chae, H.J.2016. Endoplasmic Reticulum Stress and Associated ROS. *International Journal of Molecular Sciences.* 17 : 327.

Zhang, H. and Tsao, R. 2016. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. *Current Opinion in Food Science*. 8: 33-42.

Zhang, Z., Luo, D., Xie, J., Lin, G., Zhou, J., Liu, W., Li, H., Yi, T., Su, Z. and Chen, J. 2018b. Octahydrocurcumin, a final hydrogenated metabolite of curcumin, possesses superior anti-tumor activity through induction of cellular apoptosis. *Food & Function*. 9 : 2005–2014.

Zhang, Z.B., Luo,D.D., Xie,J.H., Xian,Y.F., Lai,Z.Q., Liu, Y.H., Liu, W.H., Chen, J.N., Lai, X.P., Lin, Z.X. and Su, Z.R. 2018a. Curcumin's Metabolites, Tetrahydrocurcumin and Octahydrocurcumin, Possess Superior Anti-inflammatory Effects in vivo Through Suppression of TAK1-NF-êB Pathway. *Frontiers in Pharmacology*. 9 : 1-12.