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CURCUMIN DERIVATIVE: AN EMERGING ANTI-INFLAMMATORY AGENT

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ABSTRACT: Numerous disorders are caused by inflammation, and recent epidemics have prompted public health concerns. The fact that there are so many anti-inflammatory medications available doesn't change the fact that they frequently don't work because they pose a severe risk of gastrointestinal toxicity with both acute and chronic use, hematologic toxicity with acute use, and nephrotoxicity with chronic use. Curcumin's clinical value was, however, constrained by its low absorption. Therefore, it is crucial to find new anti-inflammatory medications, and natural products are a great place to start. One such natural substance, curcumin, is a promising therapeutic candidate because of its stability, solubility, and low toxicity. Research has indicated its inhibitory effect on prostaglandin E2 and COX-2 protein formation, as well as on phorbol ester- and CD-induced COX-2 mRNA expression and PGE2 synthesis, among other things. The mechanisms either entail inhibiting cyclooxygenases (COX) and other inflammatory enzymes. This study covers the current state of knowledge with an emphasis on the anti-inflammatory properties of curcumin and their potential molecular pathways.

INTRODUCTION: Inflammation is a healthy host immunological response to tissue damage or infection. However, persistent or unchecked inflammation can have potentially negative effects and play a role in the a etiology of a number of inflammatory diseases and malignancies. Macrophages are crucial in the inflammatory response and act as a crucial link between innate and adaptive immunity [1]. Today, a variety of NSAIDS are available for reducing inflammation and reducing pain. Still, there is an urgent need for new anti-inflammatory medications due to the serious risk of gastrointestinal toxicity with acute and chronic use, hematologic toxicity with acute use, and nephrotoxicity with chronic use. The anti-inflammatory properties of several natural substances, including herbal remedies and plant extracts, have been studied. Curcumin is a naturally occurring substance that has been studied. Its ability to inhibit cyclooxygenases (COX) and other inflammatory enzymes, as well as its ability to interfere with cell signal transduction via a variety of mechanisms, including the inhibition of protein kinase C, make it a promising candidate for an anti-inflammatory drug. For many years, medical disorders have been treated using curcumin, a natural anti-inflammatory drug. Its effectiveness as an anti-inflammatory drug has been proven in numerous experimental and pharmacologic trials [2].

In addition, curcumin is used to treat conditions such as osteoarthritis [3], cancer [4], pulmonary diseases [5], neurological disorders [6], autoimmune disorders [7], rheumatoid arthritis, Crohn's disease, diabetes and HIV [8] **Fig. 1.** The focus of research is on how curcumin derivatives work to reduce inflammation. This review will discuss the research on curcumin and its derivatives' ability to reduce inflammation.

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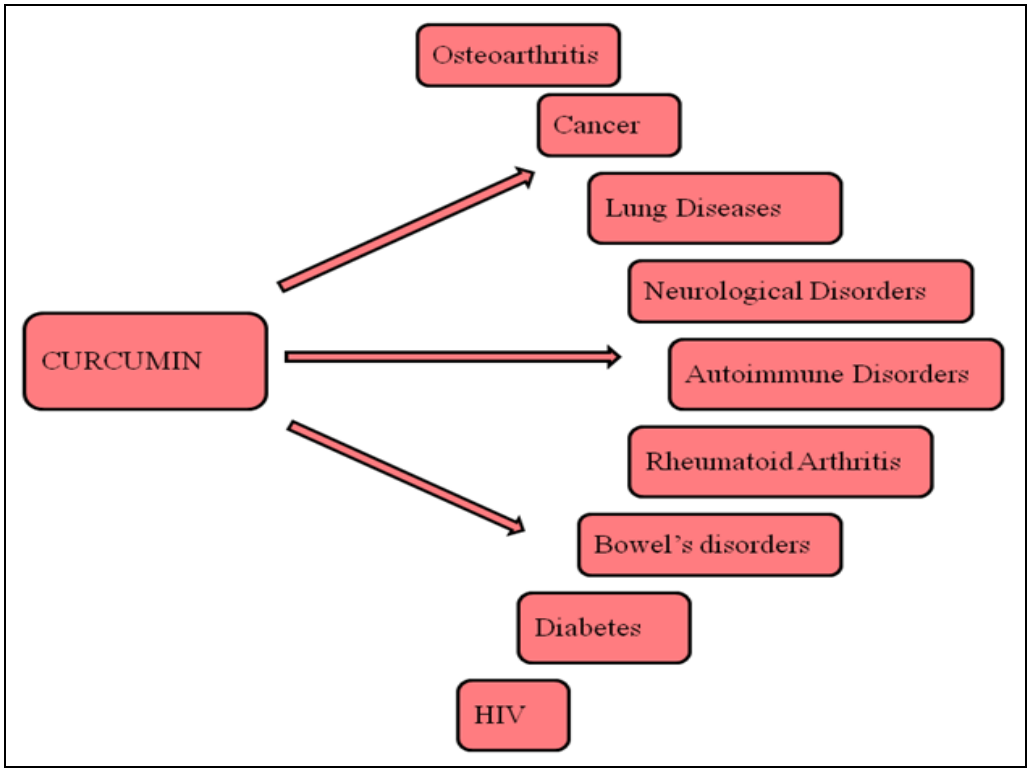

FIG. 1: CURCUMIN IN DIFFERENT DISEASES

Curcumin and its Derivatives: Curcumin is a beta-diketone that is methane in which two of the hydrogens are substituted by feruloyl groups. The primary bioactive component and colouring agent in turmeric, a curry spice made from dried, ground rhizome of the *Curcuma longa* plant, is curcumin. The ginger plant, Zingiber (which also grows in tropical Asia and the Indian subcontinent), is in the Zingiberacee family, which includes curcuma. It has been used for millennia as a seasoning in Asian cuisine and a wound-healing agent; more recently, researchers and physicians have become interested in it due to its antioxidant and anti-inflammatory characteristics, which have the potential to treat disorders including cancer and Alzheimer's disease. Curcumin is now thought to have potential benefits for treating a number of ailments. Furthermore, investigations on humans and other animal models have demonstrated that curcumin is extremely safe even at very high doses [9]. Curcumin has poor water solubility, despite being freely soluble in organic solvents like DMSO, ethanol, methanol, and acetone. Since curcumin has been a mainstay of the human diet in several nations for hundreds of years, its safety profile has already been established. Additionally, it has been used by many people to treat a variety of illnesses like diabetes, Alzheimer's disease, cancer, and rheumatic disorders.

According to reports, supplements containing curcumin may provide a wide range of health advantages, most of which are attributable to the substance's anti-inflammatory and antioxidant qualities. Curcumin is a symmetric chemical also referred to as diferuloylmethane. It has the chemical formula $C_{21}H_{20}O_6$, the IUPAC name (1E, 6E) 1, 7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione and a molecular weight of 368.38 g/mole [10]. In 1870, it was first isolated. In 1910, its chemical composition was identified. It comes in two different forms: keto and enol **Fig. 2** [11].

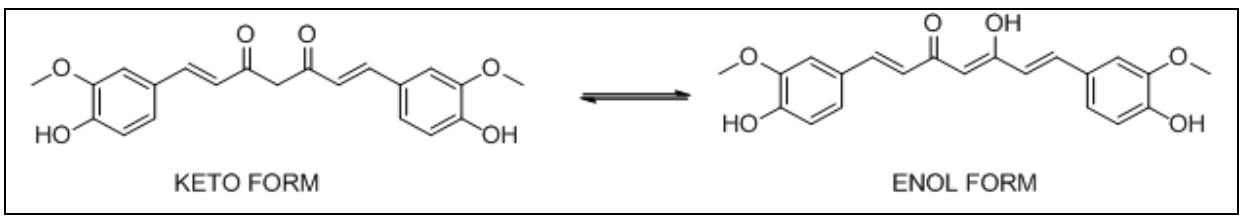

FIG. 2: CHEMICALSTRUCTURES OF CURCUMIN

Curcumin and its analogues Demethoxycurcumin (DMC) and Bis-demethoxycurcumin (BDMC) are commonly known as Curcuminoids **Fig. 3**. These curcuminoids have demonstrated strong biological activity as an antioxidant, neuroprotective, antitumor, anti-inflammatory, anti-acidogenic, radioprotective and arthritis [12].

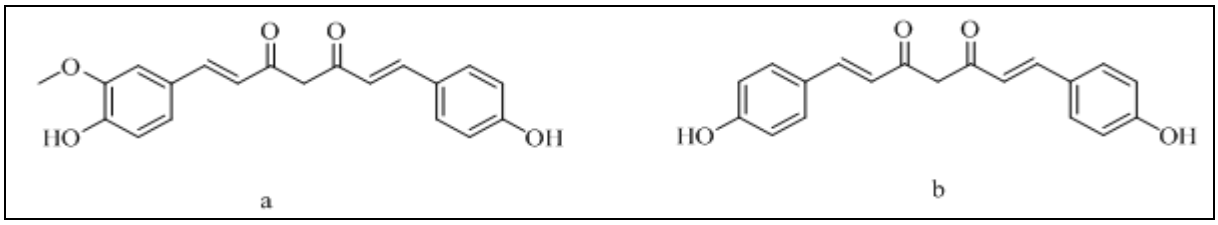

FIG 3: (A) DEMETHOXYCURCUMIN; (B) BIS-DEMETHOXYCURCUMIN

Several synthetic processes, including the Aldol reaction [13], Biginelli condensation reaction [14], Knovenegal reaction [15] and Claisen reaction [16] are used to create coumarin derivatives. The anti-inflammatory properties of derivatives of curcumin as well as potential targets and processes underlying its inhibitory actions will be explained in this review.

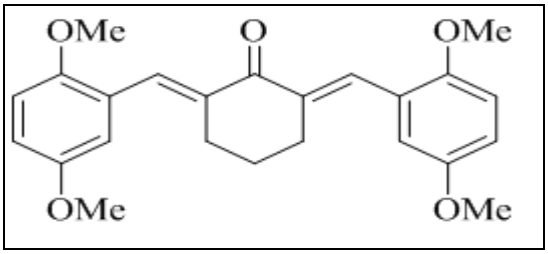

FIG. 4: BDMC33 [2, 6-BIS (2, 5-DIMETHOXY-BENZYLIDENE) CYCLOHEXANONE]

Curcumin Derivatives as Anti-Inflammatory Agents: The available therapeutic treatment for inflammatory diseases has many adverse effects (Headache, fatigue, nausea, gastrointestinal (GI), renal and cardiovascular (CV) side effects) and mostly are costly [17]. Researchers focus on synthesizing new compounds using curcumin and its derivatives to overcome the adverse effects of anti-inflammatory drugs.

In order to overcome the limitation on its bioavailability, the unstable methylene group and -diketone moiety were removed from a curcumin analogue via chemical synthesis. By reducing NO generation in the IFN-/ LPS - challenged macrophages cell, the BDMC33 [2,6-bis(2,5-dimethoxybenzylidene) cyclohexanone] displayed better anti-inflammatory actions [1] **Fig. 4.**

Different pyrane, N-phenyl-1, 3-thiazolidin, and thiocurcumin derivatives of curcumin were synthesized **Fig. 5**. The outcome demonstrated strong anti-inflammatory activity, and this compound's values were comparable to those of indomethacin. While the anti-inflammatory properties of such compounds were moderate when compared to Indomethacin [18].

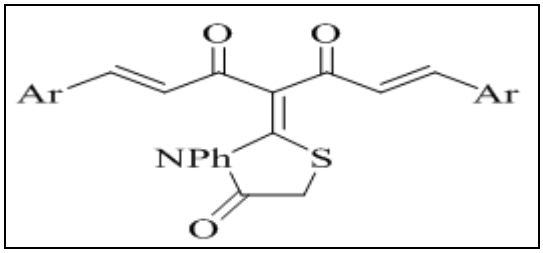

FIG. 5: N-PHENYL-1, 3-THIAZOLIDIN AND THIOCURCUMIN DERIVATIVES

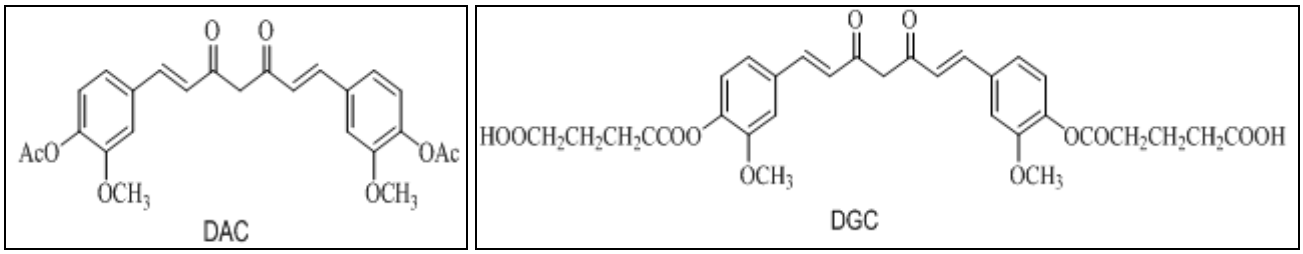

FIG. 6: STRUCTURE OF DACAND DGC

Hydrophilicity and lipophilicity are crucial for binding. Diacetyl curcumin (DAC), a hydrophilic derivative of curcumin, and diglutaryl curcumin (DGC), a lipophilic derivative, were both produced and their *in-vivo* anti-inflammatory effectiveness was compared with that of curcumin **Fig. 6**. Both

curcumin compounds showed anti-inflammatory efficacy in the carrageenan-induced paw edoema model. DAC had the highest percentage of paw edema inhibition, followed by curcumin [19].

Recently, ortho-substituted mono-carbonyl curcumin derivatives were created and tested for their ability to reduce inflammation **Fig. 7**. These derivatives replaced the curcumin's -diketone moiety with acetone, cyclopentanone, cyclohexanone, or 4-piperidione (N H, N methyl, or N acrylyl) moieties. The two active ortho-trifluoromethoxy-substituted 4-piperidione derivatives had strong anti-inflammatory action and had good cell uptake. Nitric oxide, reactive oxygen species, malonic dialdehyde, cyclooxygenase-2, interleukin-1, tumournecrosis factor, myeloperoxidase expression, and activation of mitogen-activated protein kinases and nuclear translocation of p65, were all suppressed by the derivatives [20].

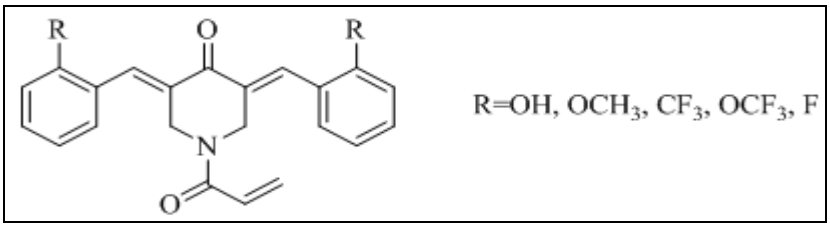

FIG. 7: ORTHO-SUBSTITUTED MONO-CARBONYL CURCUMIN DERIVATIVES

Numerous natural and semi-synthetic curcumin analogs have been found to have anti-inflammatory properties; the most effective ones were diacetylcurcumin and tetrabromocurcumin **Fig. 8.** For the anti-inflammatory activity, the -diketone moiety serving as a linker between the two phenyl groups was considered crucial [8].

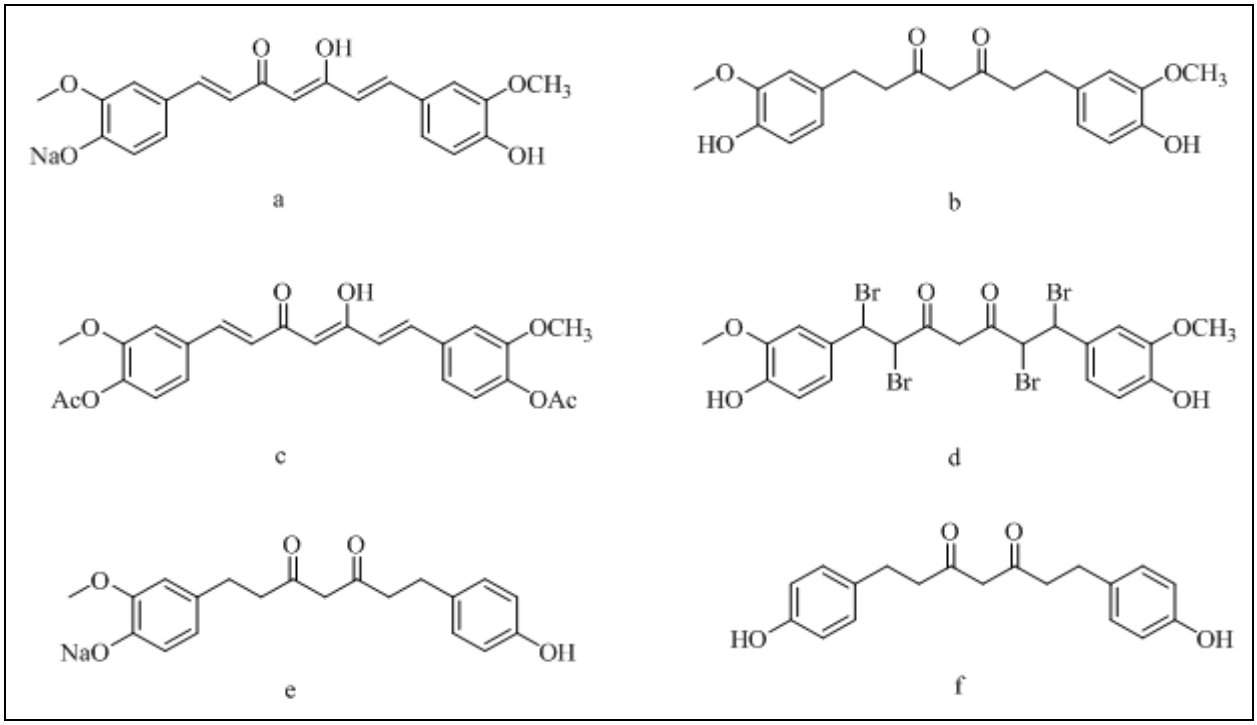

FIG. 8: (A) SODIUM CURCUMINATE (B) TETRAHYDROCURCUMIN (C) DIACETYLCURCUMIN (D) TETRABROMOCURCUMIN (E) TETRAHYDRO-DEMETHOXYCURCUMIN (F) TETRAHYDRO-BIS-DEMETHOXYCURCUMIN

Molecular Mechanism of Curcumin and its Derivatives: The activation of COX-2 protein and the production of prostaglandin E2 by CD and PMA were reduced by curcumin. Additionally, CD and PMA-induced COX-2 mRNA expression were inhibited by curcumin. Curcumin reduced phorbol ester-induced PGE2 synthesis down to nearly preinduction levels, according to *in-vitro*

experiments. ICAM-1, VCAM-1 and E-selectin expression on human umbilical vein endothelial cells was increased by TNF-a and suppressed by curcumin. The coagulation cascade begins when plasma factor VII (a) binds to tissue factor (TF). Endothelial cells do not express TF under normal circumstances. But in reaction to LPS, TNF and other biological stimuli, endothelial cells express TF. Curcumin's ability to prevent TF gene activation in cultivated endothelium cells was investigated. They showed that curcumin reduced the proteolytic degradation inhibitor protein Ik Ba's ability to prevent PMA, LPS, TNF-a and thrombin from inducing TF activity and TF gene transcription in human endothelial cells [21]. Curcumin also inhibited platelet aggregation brought on by PAF and AA, with inhibitory effects on TXA2 production and Ca^{2+} signalling, but without PKC involvement [22] **Fig. 9.**

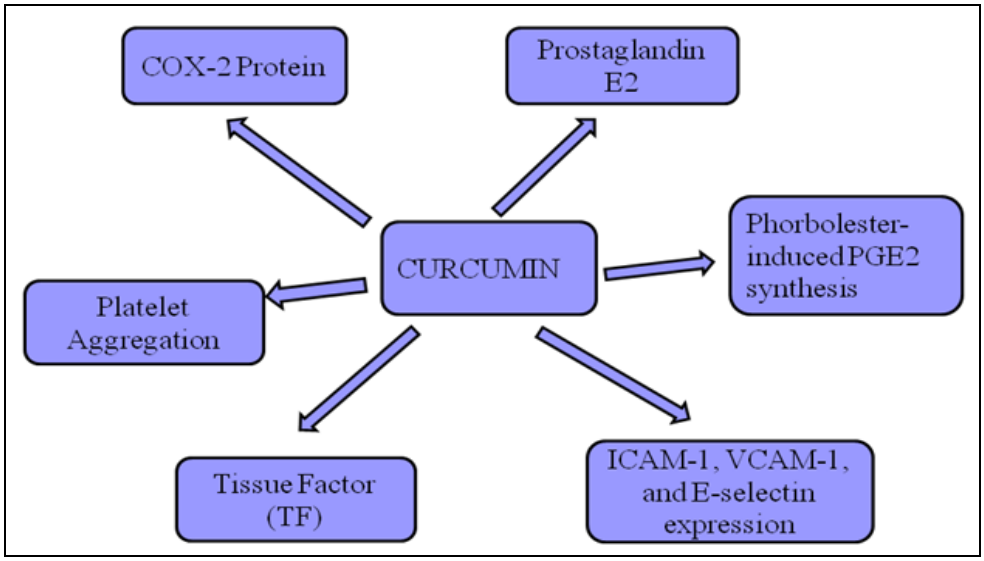

FIG. 9: CURCUMIN TARGETS FOR ANTI-INFLAMMATORY EFFECTS

CONCLUSION: In conclusion, curcumin controls NF-B, MAPK, AP-1, JAK/STAT and other signalling pathways in addition to having potent anti-inflammatory effects and reducing the generation of inflammatory mediators. Curcumin can lower inflammatory response, effectively relieve symptoms and have a role in the treatment of diseases such as IBD, arthritis, psoriasis, depression, and atherosclerosis.

Now, the substance's structural modification, preparation studies, and drug combination therapy have improved curcumin's pharmacokinetics and anti-inflammatory activities. One of these, curcumin as a dietary supplement or adjuvant medication, has a significant therapeutic impact and is currently the most practical way to apply curcumin.

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CONFLICTS OF INTEREST: Declared None

REFERENCES:

1. Zhao H, Wu L and Yan G: Inflammation and tumor progression: signaling pathways and targeted intervention. Sig Transduct Target Ther 2021; 6: 263.
2. Sharifi-Rad J, Rayess YE and Rizk AA: Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. Front Pharmacol 2020; 11: 01021.
3. Goulart M, Partar D and Cunha L: AB0792 curcumin in osteoarthritis treatment: the present state of evidence. Annals of the Rheumatic Diseases 2019; 78: 1867.
4. Das P, Roy SK, Guha A and Kuotsu K: Fabrication and comparative evaluation of curcumin and paclitaxel- loaded solid lipid nanoparticle; the pathway of effective cancer therapy. Int J Pharm Sci & Res 2020; 11(3): 1110-20.
5. Venkatesan N, Punithavathi D and Mary B: Protection from acute and chronic lung diseases by curcumin. Adv Exp Med Biol 2007; 595: 379-405.
6. Prathipati B and Rohini P: Curcumin loaded solid lipid nanoparticles enhanced efficacy in vascular dementia against homocysteine induced toxicity. Int J Pharm Sci & Res 2020; 11(8): 4053-61.
7. John JB: Curcumin and autoimmune disease. Adv Exp Med Biol 2007; 595: 425-51.
8. Elias G, Jacob PJ, Hareeshbabu E, Mathew VB, Krishnan B and Krishnakumar K: Curcumin: Transforming the

Spice to a Wonder Drug. Int J Pharm Sci Res 2015; 6(7): 2671-81.
9. Marchiani A, Rozzo C, Fadda A, Delogu G and Ruzza P: Curcuminand Curcumin-like Molecules: From Spiceto Drugs Current Medicinal Chemistry 2014; 21(2): 204-222.
10. Mahmood KO, Yasser FM, Moath KB and Mahmood HJ: Curcumin and its derivatives: a review of their biological activities. Systema Review Pharmacy 2020; 11(3): 472 81.
11. Kazakova O, Lipkovska N and Barvinchenko V: Keto-enol tautomerism of curcumin in the preparation of nanobiocomposites with fumed silica Spectrochim. Acta A Mol Biomol Spectrosc 2022; 5; 277-121287.
12. Augustine A, Anitha P and Sreerag G: Biological activities ofcurcuminoids, other biomolecules from turmeric and their derivatives. JTCM 2017; 205-233.
13. Kostrzewa T, Wołosewicz K, Jamrozik M, Drzeżdżon J, Siemińska J, Jacewicz D, Górska-PM, Kołaczkowski M, Łaźny R and Kuban JA: Curcumin and its new derivatives: correlation between cytotoxicity against breast cancer cell lines, degradation of ptp1b phosphatase and ros generation. Int J Mol Sci 2021; 22(19): 10368.
14. Movaheditabar P, Javaherian M and Nobakht V: Synthesis and catalytic application of a curcumin-based bio-MOF in one-pot preparation of tetrahydroquinazolinone derivatives *via* Biginelli reaction. Appl Organomet Chem 2022; 36(4): 6602.
15. Agarwal S, Agarwal KD, Gandhi D, Goyal K and Goya P: Multicomponent one-pot synthesis of substituted 4h-pyrimido [2,1-b] [1,3] benzothiazole curcumin derivatives and their antimicrobial evaluation. Lett Org Chem 2018; 15(10): 863-69.
16. Dunjia W, Dan W, Heng L, Hengyi D & Lian C: Synthesis and Antimicrobial Activities of Containing Sulfur Heterocyclic Curcumin Derivatives. J Med Biol Eng 2020; 1-3.
17. Harirforoosh S, Asghar W & Jamali F: Adverse effects of nonsteroidal anti-inflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci 2014; 16(5): 821-47.
18. Omyma A, Allaha A, Saghiera-El MA, Kadrya MA and Seleem AA: Synthesis and Evaluation of Some Novel Curcumin Derivatives as Anti-inflammatory Agents. Int J Pharm Sci Rev Res 2015; 32(1): 87-92.
19. James NJ, Dinesh KB, Suman B and Masoud T: Evaluation of the *in-vivo* Anti-inflammatory and Analgesic and *in-vitro* Anti-cancer Activities of Curcumin and its Derivatives. Nat Prod Commun 2013; 8(3): 359-362.
20. Wang Z, Wenwen M, Pengxiao L, Liu G and Yang J: Anti-inflammatory activity of ortho-trifluoromethoxy-substituted 4-piperidione-containing mono-carbonyl curcumin derivatives *in-vitro* and *in-vivo*. Eur J Pharm Sci 2021; 105756.
21. Smith SA, Travers RJ and Morrissey JH: How it all starts: Initiation of the clotting cascade. Crit Rev Biochem Mol Biol 2015; 50(4): 326-36.
22. Kohli K, Ali J, Ansari JM and Raheman Z: Curcumin: A natural anti-inflammatory agent. Indian J Pharmacol 2005; 37(3): 141-147.

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