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Article Review

Curcuminoid Compounds Inhibit Macrophage Migration Inhibitory Factor: *In Silico* Study for Their Association to Anti-diabetic Potency

Graciana Alves de Jesus [1], Tjie Kok [1,2*]

[1] Faculty of Biotechnology, University of Surabaya, Surabaya-Indonesia
[2] Center of Excellence for Food Products and Health Supplements for Degenerative Conditions, University of Surabaya, Surabaya-Indonesia

* corresponding author: tjie_kok@staff.ubaya.ac.id

Abstract—*Diabetes mellitus is a health problem characterized by chronic inflammation causing complications in the cardiovascular, kidneys, eyes, and nervous system, with macrophage migration inhibitory factor (MIF) protein playing a crucial function in the inflammatory process chain. MIF has been known as a signaling protein involved in the development of type 1 and type 2 diabetes mellitus (DM). There are several studies indicating that the development of type 1 and type 2 DM is influenced by the accumulation of macrophages in tissues susceptible to diabetic injury or infection. Curcuminoids, the bioactive components in turmeric, are known for their ability to decrease inflammation. This in silico study is intended to analyze the potential anti-inflammatory effect of curcuminoid in DM, with a specific focus on how it may reduce proinflammatory signals through MIF. The investigation involved predicting physicochemical, pharmacokinetic and toxicity (ADMET) qualities for curcuminoids, followed by molecular docking simulations with MIF as the target protein. The ADMET results showed curcumin and bisdemethoxycurcumin had favorable properties, while dimethoxycurcumin exhibited undesirable traits like low VDss. Therefore, molecular docking simulations were performed using curcumin and bisdemethoxycurcumin as ligands. The molecular docking simulations indicated that curcumin has a negative binding affinity slightly lower than (S, R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester (ISO-1), a reference MIF inhibitor; and bisdemethoxycurcumin binds to MIF even stronger than ISO-1, with the same interacting MIF amino acids Asn 97, Lys 32, Tyr 95, and Pro 1. Hence, the curcumin and bisdemethoxycurcumin compounds were found as having the potential to inhibit MIF activity that is associated with the progression of DM.*

Keywords: *curcuminoids, diabetes melitus (dm), inflammation, mif inhibitors, molecular docking*

Abstrak—Diabetes mellitus (DM) merupakan masalah kesehatan yang ditandai dengan peradangan kronis, yang dapat menyebabkan komplikasi pada sistem kardiovaskular, ginjal, mata, dan sistem saraf. Protein macrophage migration inhibitory factor (MIF) memiliki peran penting dalam proses peradangan. MIF diketahui sebagai protein pensinyalan yang terlibat dalam perkembangan DM tipe 1 dan tipe 2. Beberapa penelitian menunjukkan bahwa perkembangan DM tipe 1 dan tipe 2 dipengaruhi oleh akumulasi makrofag pada jaringan yang rentan terhadap cedera atau infeksi akibat diabetes. Kurkuminoid, komponen bioaktif dalam kunyit, dikenal memiliki kemampuan untuk meringankan peradangan. Studi *in silico* ini bertujuan untuk menganalisis potensi efek antiinflamasi kurkuminoid terhadap DM, dengan fokus pada kemampuannya dalam menurunkan sinyal proinflamasi melalui MIF. Studi ini mencakup prediksi sifat fisikokimia, farmakokinetik, dan toksisitas (ADMET) kurkuminoid, yang dilanjutkan dengan simulasi *molecular docking* menggunakan MIF sebagai protein target. Hasil analisis ADMET menunjukkan bahwa kurkumin dan bisdemetoksikurkumin memiliki sifat yang menguntungkan, sedangkan dimetoksikurkumin menunjukkan karakteristik yang kurang diinginkan, seperti volume distribusi (VDss) yang rendah. Oleh karena itu, simulasi *molecular docking* dilakukan dengan menggunakan kurkumin dan bisdemetoksikurkumin sebagai ligan. Hasil simulasi *molecular docking* menunjukkan bahwa kurkumin memiliki afinitas pengikatan yang sedikit lebih rendah dibandingkan dengan *(S, R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester (ISO-1)*, senyawa referensi inhibitor MIF. Sementara itu, bisdemetoksikurkumin menunjukkan ikatan yang lebih kuat dengan MIF dibandingkan ISO-1, dengan asam amino MIF yang berinteraksi yang sama Asn 97, Lys 32, Tyr 95, dan Pro 1. Dengan demikian, senyawa kurkumin dan bisdemetoksikurkumin berpotensi menghambat aktivitas MIF yang berperan dalam perkembangan DM.

Kata kunci: kurkuminoid, diabetes melitus (dm), peradangan, inhibitor mif, molecular docking.

INTRODUCTION

Diabetes mellitus (DM) is a health problem characterized by elevated glucose concentration in the blood. Autoimmune conditions, metabolic disorders, or insufficiencies in insulin production and action can bring on the disease. DM is a pandemic disease, and despite the attempts to control it, the prevalence of this disease still keeps increasing. The prevalence of DM worldwide in 2019 was predicted to be 463 million people (9.3%), with projections showing an increase to 578 million (10.2%) by 2030 and 700 million (10.9%) by 2045 [1].

DM complications are primarily caused by inflammation, with long-term hyperglycemia activating inflammatory signaling pathways, leading to organ damage and complications affecting the cardiovascular, kidney, eye, and nervous systems, typified as an inflammatory chronic illness [2]. Furthermore, type 1 and type 2 DM have association with increasing the levels of many inflammatory mediators in serum, such as MIF, TNF-α, IFN-γ, and IL-12 [3]. The study of MIF and inflammatory cytokines that cause DM is very important.

The inflammatory processes associated with type 2 DM are significantly affected by MIF, which complicates the disease pathology by elevating pro-inflammatory levels of cytokines [4,5]. Circulating high levels of MIF also contribute to autoimmune diseases such as type 1 DM [6,7]. MIF, a controversial cytokine, plays a diverse role in pathological conditions, both protective and detrimental. It is an immunomodulator and pro-inflammatory cytokine released by non-immune and immune cells as a response to various stimuli. Several studies suggest that MIF involvement in the DM pathogenesis is partly due to increased production of inflammatory molecules like IL-6, IL-1b, IL-18, TNF-a, and IL-12 [8].

These and other findings suggest MIF inhibition as a possible strategy for developing novel anti-inflammatory drugs. It is crucial to search for compounds that can inhibit MIF's activities to regulate inflammation in DM. The pharmacological properties of turmeric, *Curcuma longa* L. have been the subject of several journal publications. Studies published in journals have shown the medicinal benefits of curcuminoid compounds in turmeric rhizomes as antidiabetic [9], antioxidant [10], anti-inflammatory [11].

Other research have indicated utilizing curcuminoid substances as an antidiabetic may reduce the production of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), lipoxygenase-5, and various other pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1, and IL-8 [9,12]. A study by Hsu et al. (2025) showed that curcumin and bisdemethoxycurcumin can decrease inflammatory cytokines, and suppress intestinal inflammatory protein expression, thereby alleviating dextran sodium sulfate-induced inflammatory bowel disease in mice [13]. Similarly, Zang et al. (2019) reported that curcumin increases IL-10 level in macrophage while decreasing the those of IL-8, IL-15, IL-8, IL-6, IL-1β, and TNF-α [14]. Additionally, according to a research by Patwardhan et al. (2011) suppresses the proliferation of human and murine lymphocytes triggered by mitogens and antigens and decreases the levels of cytokines such as IL-2, IL-4, IL-6, and IFN-γ [15]. Because curcuminoids reduce the production of certain pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-8, as well suppresses the expression iNOS and COX-2, and lipoxygenase-5 may be helpful in the treatment of inflammatory illnesses in DM via inhibition of MIF activity.

The role of MIF as a potential new target of therapeutic for treating DM, where proinflammatory cytokines are involved in developing several autoimmune inflammatory diseases, including DM, is being studied in this research. *In silico* docking and activity testing is a computational method for drug design and predicting activity. It helps predict how two or more molecules bind together. This project aims to investigate whether MIF can be a therapeutic target for treating inflammation in DM. It involves testing active curcuminoid compounds *in silico* and docking them to MIF target protein to predict their binding.

MATERIALS AND METHODS

Materials

The study used a laptop hardware with Windows 11 home operating system, software Pyrex, Discovery Studio 20.0 Client (DSV 20.0), and webservers PubChem (https://pubchem.ncbi.nlm.nih.gov/), swissADME (http://www.swissadme.ch/index.php), pkCSM (https://biosig.lab.uq.edu.au/pkcsm/), and Protein Data Bank (https://www.rcsb.org/). The materials used in this study are the target protein's structure and its ligand (PDB ID: 1LJT) obtained via (RCSB) Protein Data Bank and curcuminoid compounds (curcumin, bisdemethoxycurcumin, and dimethoxycurcumin). The structure of curcumin (PubChem CID

969516), bisdemethoxycurcumin (PubChem CID 5315472), and and dimethoxycurcumin (PubChem CID 9952605) was obtained via PubChem.

Methods

Prediction of physicochemical, pharmacokinetic and toxicity (ADMET) characteristics

The chemical characteristic analysis was explained, including molecular weight (BM), logarithm of octanol/water partition coefficient (Log P), number of rotatable interatomic bonds (torsion), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), and polar surface activity (PSA). Meanwhile, the pharmacokinetic characteristics, i.e. absorption, distribution, metabolism, excretion, and toxicity characteristics were predicted using the pkCSM online tool. The SMILES canonical of the ligands were submitted to the web server of pkCSM for their toxicity and pharmacokinetic characteristics.

Target protein and ligand preparation

The preparation for MIF protein and ligand was done via Discovery Studio software. The three curcuminoid compounds, i.e. curcumin and bisdemethoxycurcumin, and dimethoxycurcumin were retrieved from the PubChem database. All these derivatives were saved in SDF format from the database of PubChem, then converted to PDB format for further *in silico* investigation using Discovery Studio software. The IUPAC names for the three compounds are presented in Figure 1. MIF protein preparation was carried out from crystallographic structure of MIF-ISO-1 (PDB ID: 1LJT) using Discovery Studio 20.0 Client by separating the protein from its ligand, and then by removing water atoms and other un-interacting protein chains.

Molecular docking and visualization of the results

Molecular docking was carried out using Pyrex software. The visualization process can be utilized to observe the interactions between MIF protein and the ligand. The Discovery Studio 2021 Client (DSV 21.0) software was used to show the visualization in two dimensions.

RESULTS

The ligands used in this research are curcumin (PubChem CID 969516) bisdemethoxycurcumin (PubChem CID 5315472), and dimethoxycurcumin (PubChem CID 9952605). The ligands structures were obtained from the PubChem (Figure 1).

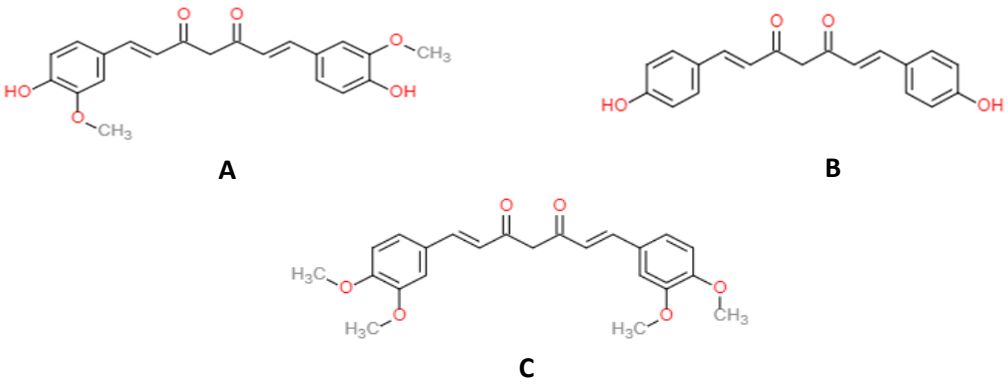

Figure 1. The ligands used in this research. Curcumin (**A**), bisdemethoxycurcumin (**B**) and dimethoxycurcumin (**C**).

Tabel 1
Physicochemical Characteristics of the Curcuminoid Ligands

Compound	WM (g/mol)	Log P	Torsion	HBA	HBD	PSA (A^2)
Curcumin	368,38	3,369	8	6	2	93,06
Bisdemethoxycurcumin	308,33	3,353	6	4	2	74,60
Dimethoxycurcumin	396,43	3,590	10	6	0	71,06

Table 1 shows Physicochemical characterizations of curcuminoid compounds were conducted using the SwissADME server. The predicted physicochemical properties including molecular weight (WM), logarithm of octanol/water partition coefficient (Log P), number of rotatable inter-atomic bonds (Torsion), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), and polar are shown below.

Table 2
Pharmacokinetic and Toxicity (ADMET) Characteristics of the Curcuminoid Ligands

Pharmacokinetic characteristics		Bioactive Compound		
		Curcumin	Bisdemethoxycurcumin	Dimethoxycurcumin
Absorption	IA (human) (%)	81,7	91,16	99,57
	CP (log Papp in 10^{-6}) (cm/s)	0,56	0,96	1,12
	SP (log Kp) (cm/h)	-3,18	-2,80	-2,95
Distribution	VDss (human) (log L/kg)	0,22	0,14	-0,56
	BBB (log BB)	-0,64	-0,09	-0,63
Metabolism	Cyp2d6 substrate	No	No	No
	Cyp2d6 inhibitors	No	No	No
Excretion	Renal OCT2 S.	No	No	No
Toxicity	Ames toxicity	No	No	No
	Hepatotoxicity	No	No	No
	Max. tolerated dose in human (log mg/kg/day)	1,21	-0,08	1,17
	Oral rat acute toxicity (LD_{50}) (mol/Kg)	1,93	2,09	1,94

Note: IA = intestinal absorption, CP = $Caco_2$ permeability, SP = skin permeability, VDss = volume distribution at steady state, BBB = blood-brain barrier.

Table 2 indicates the prediction of pharmacokinetic parameters for the curcuminoid compounds. the prediction of pharmacokinetic and toxicity characteristics is crucial for evaluating compound's potential as a promising drug candidates [16]. Rules of thumb determine the effectiveness and safety of inhibitors with specific drug and pharmacological characteristics in the human body.

Table 3
Ligand interaction with MIF Active Site

Compound	Binding Affinity (kcal/mol)	Protein	Interacting amino acid residues
ISO-1	-8,4	MIF	▪ Hydrogen bond: **Asn 97**, **Lys 32**, Ile 64 ▪ Pi stacking: **Tyr 95** ▪ Other type of bond: **Pro 1**
Curcumin	-7,6	MIF	▪ Hydrogen bond**: Asn 97**, **Lys 32** ▪ Pi stacking: **Tyr 95** ▪ Other type of bond: **Pro 1**
Bisdemethoxycurcumin	-8,6	MIF	▪ Hydrogen bond: **Asn 97**, **Lys 32** ▪ Pi stacking: **Tyr 95** ▪ Other types of bond: **Pro 1**, Ile 64

Note: **residues in bold** are of the same type of bonding as the reference compound ISO-1.

Table 3 shows molecular docking results of curcumin, bisdemethoxycurcumin, and the ISO-1 reference compound with the MIF target protein.

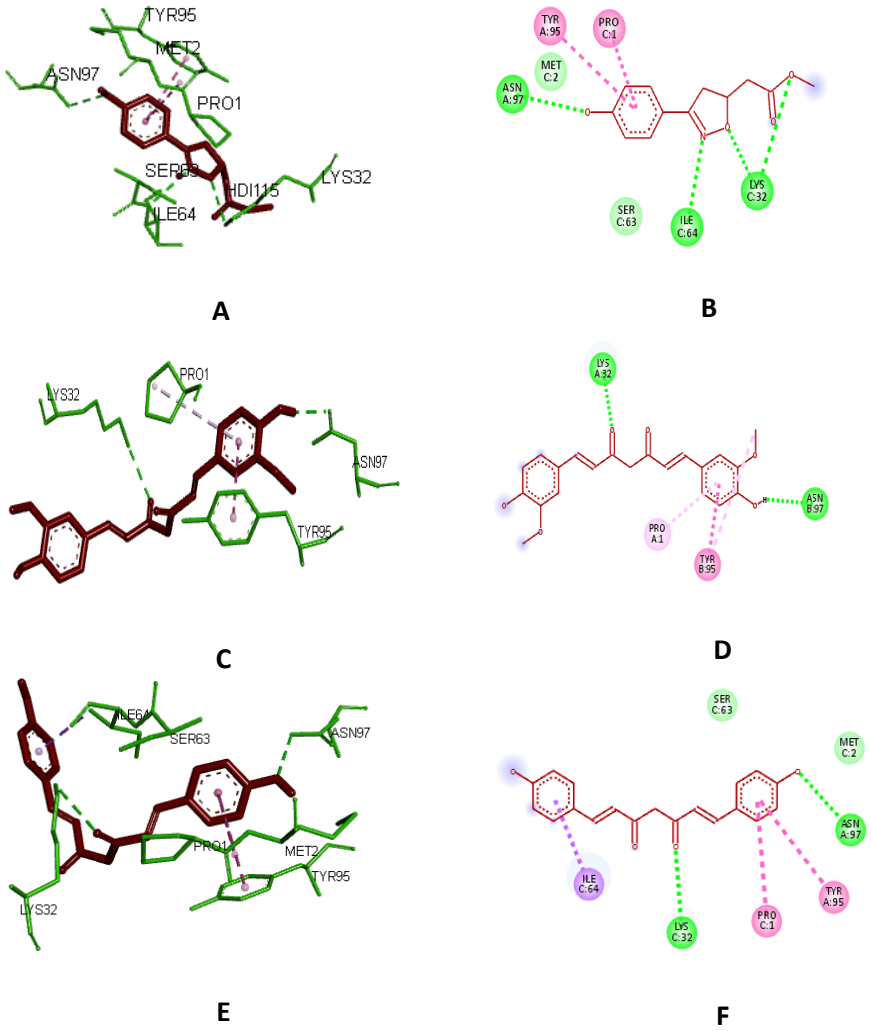

Figure 2. 3D complex and 2D MIF binding with ISO-1 (A and B), curcumin (C and D), and

bisdemethoxycurcumin (E and F).

DISCUSSION

In silico techniques have been developed to find safe and promising drug candidates and investigate possible molecular mechanisms of action between essential molecules and proteins [17]. The study utilized psychochemical, pharmacokinetic and toxicity (ADMET), and to evaluate curcuminoids activity in the human body. *In silico* study, molecular docking, could help decrease the drug failure risk in end-stage medicines by addressing directionless laboratory procedures and a lack of structural understanding of the drug and target molecule. Curcuminoid compounds, a plant-based compound with biological activities, are taken from the leaves of the *Curcuma longa* and include curcumin (diferuloylmethane), bisdemethoxycurcumin, and dimethoxycurcumin, with research aimed at exploring their therapeutic potential.

This study selected curcuminoid compounds, i.e. curcumin, bisdemethoxycurcumin, and dimethoxycurcumin as sources of anti-inflammatory and antidiabetic agents. It has been reported that several studies have shown that the active compound curcuminoids has been used to treat inflammation and diabetic rats [3].

Prediction of Physicochemical; Pharmacokinetic and Toxicity (ADMET) Characteristics

The physicochemical as well as pharmacokinetics and toxicity (ADMET) predictions were used for evaluation of the potency and toxicity of curcuminoid compounds. These predictions will provide valuable insights for drug candidates. The effectiveness of inhibitors as potential drugs is not solely determined by their antagonistic responses to protein receptors or enzymes [18]. They also require careful analysis of pharmacokinetic characteristics, such as absorption, distribution, metabolism, excretion and toxicity (ADMET) and drug similarity [19].

Rules of thumb determine the effectiveness and safety of inhibitors with specific drug and pharmacological characteristics in the human body, developed by Lipinski in 1997 for determining drug similarity [19]. According to these rules, when minimum two of these thresholds are satisfied, a drug can be orally delivered safely. Molecular weight (MW) of the molecule must be less than 500 g/mol, log P (octanol/water partition coefficient) must be less than 5, HBD (H bond donor) must be less than 10, HBA (H bond acceptor) must be <5, and ranges TPSA (topological polar surface area) must be < 140 A^2 [20]. The corresponding values of curcumin, bisdemethoxycurcumin and dimethoxycurcumin showed that there is no violation of Lipinski's rule (Table 1).

Prediction of pharmacokinetic and toxicity characteristics is crucial for evaluating potential of a compound as a promising candidate of drug [16]. Rules of thumb determine the effectiveness and safety of inhibitors with specific drug and pharmacological characteristics in the human body. The ADMET prediction is used to assess The ADMET prediction is used to assess absorption ligands, distribution ligands, metabolism ligands, excretion ligands, and toxicity of ligands. Table 2 shows the ADMET prediction results.

Absorption

The pkCSM platform was used to collect data on intestinal absorption [% absorbed], Caco-2 permeability [log Papp in 10^{-6} cm/s] and skin permeability [log Kp] in order to evaluate the absorption capacity of curcuminoids compound. The study evaluated characteristics such as intestinal absorption, skin permeability, and $Caco_2$ permeability to investigate the absorption characteristics of certain ligands. Intestinal absorption measures a molecule's absorption in the intestine, with poorly absorbed compounds having a percentage below 30% and well absorbed ones having a percentage above 80% [21]. Curcumin, bisdemethoxycurcumin, and dimethoxycurcumin were absorbed well with the predicted intestinal absorption higher than 80%.

Another important factor for certain drugs' efficacy is the $Caco_2$ permeability parameter. Drug absorption is typically evaluated using a $Caco_2$ cell monolayer, as Caco-2 cells closely resemble human intestinal epithelium. This method is preferred as the intestine is the primary site for absorption of orally administered drugs, making it crucial to assess the extent of compound absorption at this location [22]. The proportion of the compound absorbed is determined using this method. High $Caco_2$ permeability is indicated by a molecule with a log Papp of 10^{-6} cm/s and a predictive value over 0,90 cm/s [23]. The predicted log Papp value shows that the curcuminoid compounds have high Caco2 permeability, indicating their potential for oral absorption through the intestinal mucosa, as per the predicted results.

For topical applications, the recommended skin permeability value (log K_P) is greater than -2,50 cm/h, which is important for drug efficacy and is highly relevant for transdermal drug delivery [24]. The log K_P value for each curcuminoid compound ranged from -2,76 cm/h to -2,80 cm/h. Since all the curcuminoid compounds have a high level of skin penetration, i.e. can easily penetrate the skin, they are suitable for topical applications or transdermal drug delivery systems. Good skin permeability can be used as considerations for the development of new drugs with transdermal administration.

Distribution

The volume of distribution (VDss) and blood-brain barrier (BBB) permeability are the parameters considered for the drug candidates' distribution. The steady state volume of distribution (VDss) is the theoretical volume of a substance that needs to be uniformly distributed to have the same concentration as in blood plasma. The higher the VDss, the more substance is distributed in tissue, potentially influenced by renal failure and dehydration [16]. Log VDss < -0.15 indicates low distribution, while Log VDss > 0.45 indicates high distribution. Table 2 shows the VDss value of curcumin and bisdemethoxycurcumin is 0,22 L/kg and 0,14 L/kg, respectively, i.e. within the recommended range except dimethoxycurcumin, with a very low VDss value of -0,56 is more likely to remain in blood plasma rather than being distributed to body tissues. A low VDss indicates that a larger proportion of the drug remains in the bloodstream, either due to high solubility in water or strong binding to plasma protein. In contrast, a high VDss implicates significant distribution to tissues, often as a result of binding to tissue or high solubility in lipid [25].

Drugs' permeability to the blood-brain barrier (BBB) is crucial factor for increasing efficacy and decreasing side effects. Permeability is assessed in vivo via log BB, the ratio of brain concentration to plasma's. The compound's efficiency to penetrate the blood-brain barrier is indicated by a log BB value > 0,30; while its distribution is not well defined if log BB < -1 [26]. The three curcuminoid compounds cannot cross the BBB as their log BB values are below 0.3. Compounds with log BB > 0.3 can penetrate the barrier, while those with log BB < -1 cannot [16, 26].

The BBB is a defense mechanism made up of tightly joined endothelial cells that regulate the penetration of substances from the blood circulation into the brain. In this context, determination of permeability across the BBB is crucial in assessing a substance's ability to reach its target in the brain. This mechanism also plays a role in increasing efficacy, decreasing toxicity and side effects of substances designed for treatment within the central nervous system [26].

Metabolism

Cytochrome P450, a vital detoxifying enzyme found in the liver, plays a crucial role in oxidizing foreign organic substances and facilitating their excretion. This study assesses the ability of substances that can inhibit cytochrome P450, specifically the CYP2D6 isoform. All the curcuminoid compounds are not inhibitors of CYP2D6 (Table 3), suggesting that they do not influence this enzyme and are probably metabolized by P450 enzymes [26].

Excretion

Substance excretion is the process of elimination of substances or their metabolites from the body. Renal organic cation transporter 2 (renal OCT2) is a crucial renal transporter involved in substance removal and clearance through the kidneys, but its substrates can potentially cause adverse interactions with OCT2 inhibitors. When OCT2 inhibitors and OCT2 substrates are given together, there is a chance that they may interact negatively (16). According to predictions, no curcuminoid compound affects the OCT2 substrate, so it is predictable that there will be no side effects of curcuminoid in this case.

Toxicity

To evaluate the compounds toxicity in this study, Ames toxicity, hepatotoxicity, the maximum recommended tolerated dose (MRTD), acute oral toxicity in rats (LD_{50}), and maximum hepatotoxicity in humans can be conducted (Table 2).

Predicting compounds toxicity is crucial in the design of drug development, and computational toxicity estimates are better than animal toxic dose determination and can decrease animal experimentation [27]. Three important parameters were predicted based on PkCSM analysis results, namely Ames toxicity, potential hepatotoxicity, oral rat acute toxicity (LD_{50}) (mol/kg), and the maximum tolerated dose in humans (Table 2).

Ames toxicity is used to estimate the carcinogenicity of drug compounds. None of the compounds showed ames toxicity. Oral Rat Chronic exposure to low-dose substances over time is a significant concern in treatment strategies. High acute toxicity is considered when LC_{50} value below 0,50 mM (LC_{50} log < -0,30 mol/Kg) [16]. The results show that all curcuminoid compounds are not toxic.

MRTD is a human dosage threshold that informs the initial dose for medicines in clinical trials phase I, based on animal studies. A MRTD of ≤ 0,477 log(mg/kg/day) is regarded as low, and high if > 0,477 log(mg/kg/day). The MRTD values for curcumin, bisdemethoxycurcumin and dimethoxycurcumin are 1,21, -0,08; and 1,17 respectively, meeting the criteria for low toxicity and ensuring they do not cause intolerable toxic effects in test subjects, as per the given criteria [24, 16]

The study confirmed the satisfactory physicochemical, pharmacokinetics, and non-toxicity of curcumin and bisdemethoxycurcumin, while dimethoxycurcumin showing unsuitable aspects like low VDss parameters. Hence, the two compounds, i.e. curcumin and bisdemethoxycurcumin, showed potential for oral use in therapeutic applications, and were selected for molecular docking with MIF target protein to determine their interaction with amino acid residues of MIF and the binding affinity.

The Docking of Curcuminoid Compounds with MIF Target Protein

Using protein-protein docking techniques to understand the interaction between MIF and curcuminoids. The interaction between possible inhibitors and MIF has been studied using molecular docking. MIF is a target for drug discovery because it acts as protein target in several kinds of inflammatory illnesses, such as type 1 and type 2 DM.

In consideration of the anti-inflammatory effects in DM, it could be expected that curcuminoid compounds could provide some therapeutic effects in diabetic diseases. According to a study, curcuminoid compound can lessen the harm caused by DM by controlling inflammation in the diabetic rats' brains [28]. Hence, curcuminoid compounds were utilized in molecular docking experiments to investigate the mechanism of curcuminoid derivatives more. Based on the analysis of physicochemical and pharmacokinetic characteristics, both curcuminoids, namely curcumin and bisdemethoxycurcumin, exhibited promising ADMET properties (Table 1 and 2). Therefore, we proceeded with molecular docking to evaluate their interaction with MIF and their binding affinities. Furthermore, based on the theory that a MIF is one target in proinflammatory cytokine activity, we used the molecular docking experiment to verify that hypothesis.

In this study, molecular docking was conducted using ISO-1 inhibitor as a reference compound or comparison ligand because ISO-1 is the well-known MIF inhibitor, which has been thoroughly investigated in several experimental disorders. By binding to the tautomerase active site of MIF, ISO-1 inhibits MIF signaling downstream [29]. Type-2 DM db/db mice treated with ISO-1 can significantly reduce albuminuria, blood glucose, epithelial-mesenchymal transition (EMT), extracellular matrix accumulation, and infiltration of macrophage in diabetic kidneys [30]. Moreover, ISO-1 can also inhibiting the cell pyroptosis and NLRP3 inflammasome signaling pathway, thus protect against experimental AKI [31,32]. These findings highlight the feasibility of targeting the inhibitors-MIF receptor interaction by the curcuminoid compounds and support the therapeutic value by inhibiting inflammation activity of MIF protein in the progression of DM.

Curcumin has a binding affinity of -7,6 kcal/mol slightly lower than ISO-1 MIF inhibitor reference (a binding affinity of -8,4 kcal/mol), whereas bisdemethoxycurcumin has a more negative binding affinity of -8,6 kcal/mol, i.e. stronger interaction than the ISO-1 reference (Table 3). This suggests that both curcuminoid compounds can decrease pro-inflammatory activity by inhibiting MIF function.

Based on the crystallographic structure of MIF-ISO-1 (PDB ID: 1LJT), the interacting residues of the MIF protein with ISO-1 reference compound are Ile-64, Lys-32, Pro-1, Tyr 95 and Asn-97 [29]. The docking results with all the ligands indicate that there is no major conformational change upon inhibitor binding. 2D docked conformations show that the curcumin and bisdemethoxycurcumin compounds bind in the active site like ISO-1, with several similar amino acid residues involving in the interactions, i.e. Asn 97, Lys 32, Ile 64, Tyr 95, and/or Pro 1 (Figure 2A-2F). Previous study demonstrated a strong relationship between the suppression of MIF tautomerase activity by ISO-1 and the inhibition of MIF proinflammatory activity [29]. Hence, the curcuminoid compounds, i.e. curcumin and bisdemethoxycurcumin contained sin turmeric could potentially be used as the inhibitors of MIF activity that is associated with the progression of DM.

CONCLUSION

This study highlights the potential of curcuminoids, particularly curcumin and bisdemethoxycurcumin, as anti-inflammatory agents for managing diabetes mellitus (DM). The ADMET analysis revealed that curcumin and bisdemethoxycurcumin exhibit favorable properties, whereas dimethoxycurcumin showed undesirable traits. Molecular docking simulations showed that both curcumin and bisdemethoxycurcumin have promising binding affinities to MIF, a key protein involving in the inflammatory process of DM. Bisdemethoxycurcumin showed even stronger binding than the ISO-1 MIF inhibitor reference. These findings suggest that curcumin and bisdemethoxycurcumin could potentially inhibit MIF activity and potentially reduce the progression of DM.

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