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In Silico Evaluation for the Inhibitory Action of Curcumin Derivatives on the CD14 Proteins

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Abstract

Background: Autoimmune thyroid diseases (AITD) are a class of immune disorders that target the thyroid gland. Two forms of the disease predominate: Graves' disease and Hashimoto Thyroiditis. The major symptoms of the diseases include hyperthyroidism and hypothyroidism, respectively. **Objectives:** One target protein of the immune system that is a hot spot in drug discovery is the CD14 protein (or cluster of differentiation 14). CD14 is a cell membrane protein that is highly expressed in macrophages, monocytes, and neutrophils and is a crucial receptor for gram-negative lipopolysaccharide (LPS). The CD14 monocytes produce high levels of HLA-DR, which may contribute to AITD. Single Nucleotide Polymorphisms (SNPs) in CD14 were previously identified to be risk factors to GD and HT diseases. However, the mechanistic involvement of CD14 protein or its relation to the AITD is not yet clear. **Methods:** In this study, the researchers shed light on targeting CD14 protein in silico for the aim of alleviating autoimmune thyroid diseases. Docking experiments and ADME/Tox (Absorption, distribution, metabolism and elimination) properties were performed to predict the mechanistic insights for the plausible inhibitory effect of recently produced synthetic derivatives of curcumin on CD14, as well as the estimation of drug likeness and bioavailability. **Results:** Most of the compounds showed variable levels of inhibition on the CD14 protein and good bioavailability scores. **Conclusion:** The results indicated that curcumin derivatives could be effective drugs against auto-immune thyroid diseases.

Keywords: Area of Interest: Drug Discovery, Docking, Structural bioinformatics, chem-informatics

1. Introduction

Autoimmune thyroid diseases (AITD) are a set of ailments that target the thyroid glands [1]. Two of the most prevalent forms of the AITD diseases are the Graves' Disease (GD) and Hashimoto Thyroiditis (HT), which cause hyperthyroidism and hypothyroidism, respectively [2]. More clearly, patients with Graves' Disease (GD) may suffer from anxiety, increased sensitivity to heat, weight loss, among other symptoms [3]. The prevalence of GD is 24.8 per 100,000 population per year [4], and it ranges from 21 per 100,000 population to 120 per 100,000 population per year [5]. Patients with Hashimoto Thyroiditis (HT) disease, on the other hand, suffer from fatigue, increased sensitivity to cold, increased sleepiness, muscle weakness, plus many other symptoms [6]. HT ranges from 27 per 100,000 per year to 448 per 100,000 per year in general populations [5].The older ages and females normally show higher incidence of the diseases [7].

As is the case for many diseases, genes and some environmental factors increase the susceptibility and predisposition of AITD. Several genes were characterized to be connected to AITD, including the HLA-DR gene locus and the non-MHC genes, e.g., CD14, CD40, CTLA-4, PTPN22, thyroglobulin, and TSH receptor genes [8, 9]. The major environmental triggers of AITD include iodine, infection, medications, smoking, and stress [10].
GD and HT diseases are caused by a faulty outbreak for the autoantibodies of the immune system against the thyroid gland. This attack by GD or HT results in an increase in the thyroid gland volume and a consequent increase in thyroid hormones or a decreased thyroid volume and a decrease in thyroid hormones, respectively. Complications of GD include problems with fertility, the menstrual cycle, as well as pregnancy. Additional complications are heart failure, muscles problems, palpitations, and thinning bones [3]. HT is associated with heart disease, heart failure, high blood pressure, and high cholesterol [6].

CD14 (or cluster of differentiation 14) is a membrane cell-surface protein that is highly expressed on monocytes, macrophages, and neutrophils [11]. However, it is lowly expressed on other hematopoietic and stromal cells. CD14 is a recognition receptor of the innate immune system. It recognizes gram-negative cells and acylated microbial products and alerts the immune cells to their presence [12, 13]. The CD14 monocytes have been shown to express high levels of HLA-DR, which may cause AITD [14]. Several SNPs in CD14 gene were found to be associated with the genetic predisposition to GD with a statistical significance in the analysed populations [8]. In a study by Xin and colleagues, genome-wide methylation was compared between GO patients and negative controls. Differential methylation was detected in 148 loci, among which CD14 was a major gene [15]. Other studies concluded an enrichment of monocytes with CD14 and TLR2 expressions in HT disease compared to healthy controls [16, 17]. Thus, to treat AITD, specialists can use drugs that reduce the levels of CD14.
Numerous routes are followed to alleviate AITD, where the production of thyroid hormones or their effects are aimed at being blocked. Patients with Graves' disease (including pregnant women) are administered medications like 6-n-propyl-2-thiouracil (PTU) that stop the production of the thyroid hormone [18]. Additionally, Graves' disease can be treated by beta-blockers, inorganic iodide, and lithium. Beta-Blockers can decrease the symptoms of hyperthyroidism [19]. Inorganic iodide could decrease the vascularity of the thyroid gland. As a result, it can be administered prior to surgery [20]. When drugs and radioactive iodine fail to treat the diseases, surgical intervention is followed, where all or part of thyroid gland is removed [21]. Levothyroxine (LT4) and hormone replacement therapy (via the introduction of triiodothyronine (T3)) may be prescribed to treat the Hashimoto Thyroiditis [6].

A few anti-thyroid drugs , such as amiodarone, carbimazole, and propylthiouracil, are confined by their narrow action and pharmacokinetic effect and have side effects. Traditional medicine utilizes herbal-based remedies by about 80% of the world's population. A wide range of herbal-derived compounds or chemically modified herbal phytochemicals are used to produce safe pharmaceutically active drugs with reduced or no side effects [22, 23].

Curcumin is a phytopolylphenol pigment produced by the plant turmeric of the ginger family (Curcuma longa) and other *Curcuma* species. *Curcuma longa* has been traditionally used in the Middle East and the Far East in traditional medicine due to its anticancer, anti-inflammatory, antimicrobial, anti-mutagenic, and antioxidant properties [24, 25]. Exemplary antioxidants present in turmeric include curcuminoids, used to alleviate oxidative stress and other illnesses including COVID19 [26-29].

Curcumin was shown to play a major role in the treatment of AITD by regulating inflammatory cytokines, such as IL-1beta, IL-6, IL-12, TNF-alpha and IFN-gamma. Curcumin was also linked to several pathways in immune cells including the JAK-STAT, AP-1, and NF-kappaB signalling pathways [30].

The process of drug discovery is time, money and effort consuming. Normally, it takes 10 to 14 years to launch a new drug on the market. The cost of a new drug ranges between $300 million and $2.8 billion dollars [31]. Using docking in drug discovery can decrease the time, money and efforts needed to launch a new drug [32].

Docking acts at the atomic resolution for the screening of robust ligand-protein interactions. Several calculation are carried out that help in resolving the ligand orientation, inhibition constants, as well as the binding affinities [33]. Additionally, drug likeness and bioavailability help to understand drug likeness via studying the ADME (Absorption, distribution, metabolism and elimination) properties of the drug [34, 35]. In this study, docking protocols and ADME/Tox studies were carried out to demonstrate the effects of several phytochemicals in the curcumin extract on CD14 molecule. To achieve this purpose, the researchers used the crystal structure of human soluble CD14 (PDB ID: 4GLP) [13].

2. Materials and Methods

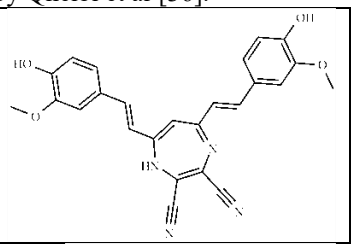
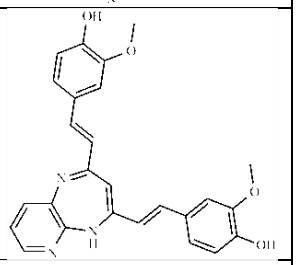
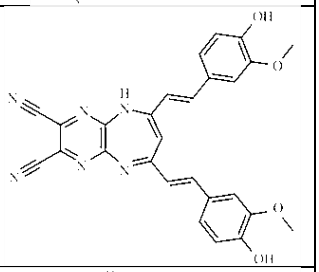
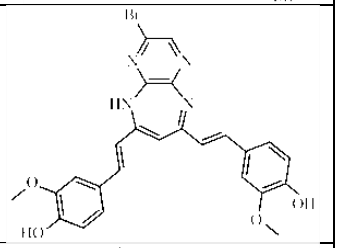
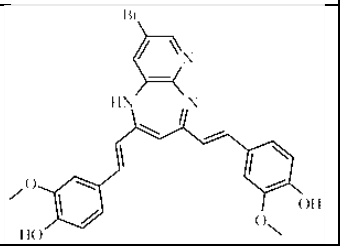
The researchers based the study on docking novel curcumin derivatives, which were synthesized by Qneibi et al. (Table 1)[36]. Herein, input PDB files were set up. To this aim, the SMILES structures of the compounds were processed based on the systemic IUPAC structures[37]. The Open Babel server was used to generate the PDB structures[38]. The compounds were docked against the apo form for the CD14 protein (PDB: 4GLP)[13] using the AutoDock Vina program, version 4.2[39]. AutoDock Vina is considered among the software choices with best scores for docking and top-ranked qualities[40].

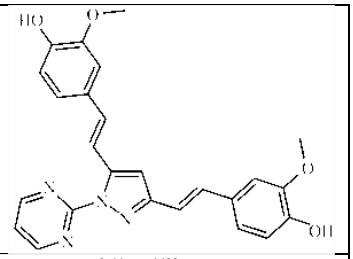
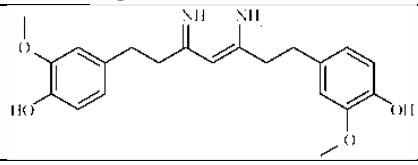
In each docking experiment, the receptor protein was kept rigid. Polar hydrogen atoms were added to the protein structure and heteroatoms were removed. Input files for docking were prepared using the AutoDock tools[39]. Parallel rectangular grid boxes of 50Å×50Å ×80Å dimensions were prepared. The center of the grid was based on the center of mass of the protein. Starting from random coordinates, 20 independent docking runs were performed for the protein against each compound using the Lamarckian genetic algorithm[41]. The initial maximum energy was set to zero, and up to 1000 retries were permitted. The genetic algorithm employed a population size of 150 and a maximum of 2,500,000 energy evaluations. A total of 27,000 generations were executed. The mutation and crossover rates were fixed at 0.02 and 0.8, respectively, with a window size of 10. Local optimization was carried out using the Solis and Wets method for 300 iterations. The thresholds for

consecutive successes and failures before adjusting the step size (rho) were both set to 4. The Cauchy distribution parameters were assigned as $\alpha = 0.0$ and $\beta = 1.0$. The resulting PDB files were extracted after the runs. Docking results were assessed as the best fit of the ligand-protein interactions in each of the compounds.

As a part of the process of drug discovery, the researchers used SwissADME to evaluate the pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry friendliness of the ligands. Molecules are input by drawing them using a molecular sketcher or by adding SMILES structures[42]. Accordingly, SwissADME then predicts several physicochemical properties[42]. One major property in the prediction of bioavailability is the Lipinski's rule of five (RO5)[43, 44]. The rule states that poor absorption is more possible when there are more than 5 H-bond donors, the ligand weighs over 500 daltons, the log P partition coefficient (octanol/water) is above 5, the molecule has more than 10 H-bond acceptors and more than 10 rotatable bonds. Violation of three or more rules decreases the chance or oral bioavailability. Yet, several orally administered drugs violate two to three rules[45].

Table 1. The seven curcumin derivatives introduced by Qneibi et al [36].

(a) S1: 5,7-bis[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-1H- 1,4-diazepine-2,3-dicarbonitrile	
(b) S2: 4-[(E)-2-(2-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]- 5H-pyrido[2,3-b][1,4]diazepin-4-yl}ethenyl]-2-methoxyphenol	
(c) S3: 6,8-bis[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-5H- pyrazino[2,3-b][1,4]diazepine-2,3-dicarbonitrile	
(d) S4: 4-[(E)-2-(3-bromo-8-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]- 5H-pyrazino[2,3-b][1,4]diazepin-6-yl}ethenyl]-2-methoxyphenol	
(e) S5: 4-[(E)-2-{8-bromo-4-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]- 1H-pyrido[2,3-b][1,4]diazepin-2-yl)ethenyl]-2-methoxyphenol	

(f) S6: 4-[(E)-2-(5-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-1-(pyrimidin-2-yl)- 1H-pyrazol-3-yl}ethenyl]-2-methoxyphenol	
(g) S7: 4-[(4Z)-5-amino-7-(4-hydroxy-3-methoxyphenyl)-3- iminohept-4-en-1-yl]-2-methoxyphenol	

3. Results

3.1. Binding Free Energies and Inhibition Constants for CD14 Protein

The binding free energies, inhibition constants as well as the root mean square deviation (RMSD) values for the ligand structures upon docking to the reference structures are shown in table 2. The inhibition constants (Ki) for the CD14 binding interface to the S1 – S3, S5 – S6 ligands were in the range (1.19 - 10.26 µM), with higher values of inhibition constants for the CD14:S4 and CD14:S7 interfaces (Ki = 234.97, 463.37 µM, respectively). Binding free energies of the CD14 protein to the several curcumin derivatives were in the range of (−4.55 - −8.08 Kcal/mol). The root mean square deviations (RMSD) of the ligand crystal structures from the reference ones were in the range of (32.05-78.63 Å), except for S4, with an unidentified value.

Table 2. Binding free energies, inhibition constants and RMSD values for the binding interfaces of the best fit between S1-S7 ligands and the CD14 protein.

Protein	Ligand	AutoDock binding free energy (Kcal/mol)	AutoDock inhibition constant, Ki (µM)	RMSD for the ligand from the reference structure (Å)
CD14	S1	-7.23	4.99	67.859
	S2	-6.81	10.26	66.001
	S3	-7.66	2.43	32.054
	S4	-4.95	234.97	-
	S5	-7.09	6.34	73.609
	S6	-8.08	1.19	69.522
	S7	-4.55	463.37	78.630

3.2. Binding Interface for the CD14 Protein

For the CD14 protein (PDB ID: 4GLP) [13], and in all seven ligand-protein interaction interfaces, moderate-ranged (3.6 - 4.0 Å) electrostatic interactions had higher contribution than the short-ranged (2.5 - 3.5 Å) interactions at the ligand-protein interface in the binding energies (Figure 1). Few longer bonds contributed to the binding process at the binding interface. Nonpolar amino acids at the binding interfaces were prominent (e.g., Leu, Pro, Trp, Phe, Val, and Ala). These amino acids were more noticeable at the binding interfaces for all phytochemicals, with the least contribution at the S2:CD14 interface. Additionally, several polar contacts were found at the binding interfaces (e.g., Asn, Arg, Ser, Arg, Glu, Gln, Asn and Lys) for all phytochemicals excepting at the S5:CD14 interface, which was totally established by non-polar contacts.

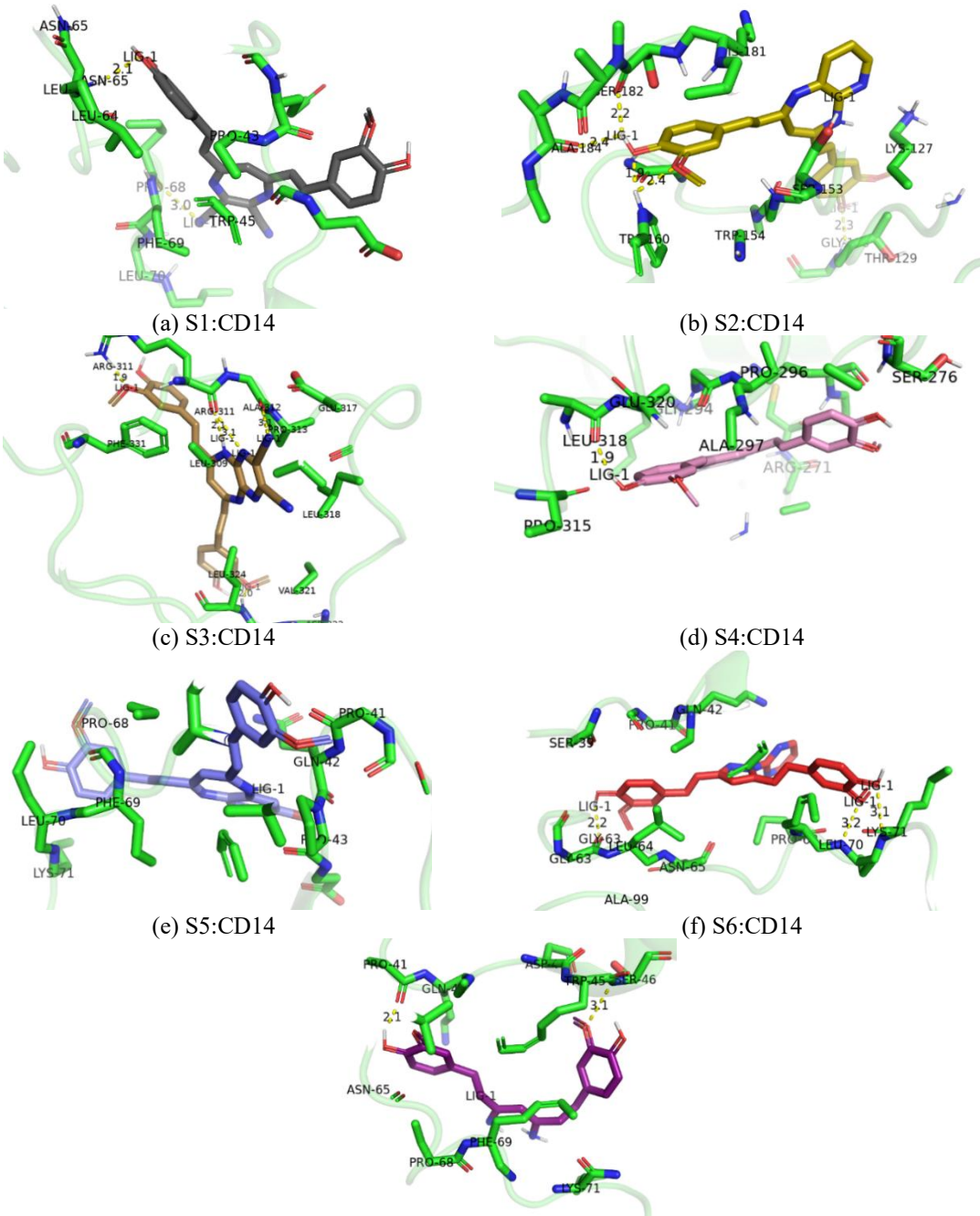


Figure 1. Binding interfaces for the curcumin derivatives to the CD14 protein (PDB ID: 4GLP [13]). (a) S1-CD14; (b) S2-CD14; (c) S3-CD14; (d) S4-CD14; (e) S5-CD14; (f) S6-CD14; (g) S7-CD14. Yellow color was used for polar contacts, while blue color for nonpolar ones.

3.3. ADME/Tox and Bioavailability of the Seven Ligands

Drug likeness was evaluated via examining the ADME properties. For a ligand to have the properties of a successful drugs, it is expected to have a good solubility, to obey the Lipinski's rule of 5 (RO5). Additionally, it is expected not to inhibit CYP450 enzymes or to cause problems related to elimination or excretion [46]. Table 3 shows that all seven ligands obey the Lipinski's RO5; with no violation (S1-S3, S6, S7) or at most one violation

(S4, S5), where the latter two molecules slightly exceeded the maximum molecular weight of 500 g/mol. Since none of the molecules broke three or more of the Lipinski's RO5, all ligands are orally active [43, 44].

Table 3. ADME analysis -Physicochemical properties (Lipinski rule of five of ligands)

Phytochemical	Physicochemical properties (Lipinski rule of five)					
	Molecular weight (g/mol)	H-bond acceptor	H-bond donor	Log P	No of rotatable bond	Lipinski
S1	440.45	7	3	2.88	6	Yes (0 violations)
S2	441.48	6	3	3.86	6	Yes (0 violations)
S3	492.49	9	3	3.07	6	Yes (0 violations)
S4	521.36	7	3	4.07	6	Yes (1 violation; MW >500)
S5	520.37	6	3	4.48	6	Yes (1 violation; MW >500)
S6	442.47	7	2	3.57	7	Yes (0 violations)
S7	370.44	5	4	3.04	9	Yes (0 violations)

To measure the ratio of an orally administered compound that passes to the systemic circulation, the bioavailability score was used (see table 4). It ranges from 0 to 1, where higher scores indicate higher fractions of the ligands to reach the systemic circulation. The researchers examined the five phytochemicals that showed the good docking results (S1 – S3, S5 – S6) as well as the other two phytochemicals for their bioavailability scores. All showed an intermediary bioavailability score (0.55). However, the prediction of aqueous solubility by three methods: ESOL logD, (ALI) logS, and (SILICOS- IT) logS presented moderate to poor solubility for the vast majority of phytochemicals [42].

During their first pass to the liver, a great percentage of drugs are metabolized by Cytochrome P450 enzymes, in a condition called the first pass effect [47]. In screening CYP450 inhibitors, all seven phytochemicals showed possible inhibition of some CYP450 enzymes. The inhibition of these enzymes by the selected ligands proposes a contribution to the drug-drug interaction [48].

Table 4. Drug-likeness analysis of bioactive compounds

Phytochemical	Bioavailability score	Solubility			Pharmacokinetics	
		Log S (ESOL)	Log S (Ali)	Log S (SILICOS-IT)	GI absorption	CYP enzymes inhibitors
S1	0.55	Moderately soluble	Poorly soluble	Moderately soluble	High	CYP2C19, CYP2C9, CYP3A4
S2	0.55	Moderately soluble	Poorly soluble	Poorly soluble	High	CYP2C19, CYP2C9
S3	0.55	Moderately soluble	Poorly soluble	Poorly soluble	Low	CYP2C9, CYP3A4
S4	0.55	Poorly soluble	Poorly soluble	Poorly soluble	High	CYP2C19, CYP2C9

S5	0.55	Poorly soluble	Poorly soluble	Poorly soluble	High	CYP2C19, CYP2C9,
S6	0.55	Moderately soluble	Poorly soluble	Poorly soluble	High	CYP2C9
S7	0.55	Soluble	Moderately soluble	Moderately soluble	High	CYP2C9, CYP2D6, CYP3A4

4. Discussion

Curcumin derivatives were lately synthesized by Qneibi and coworkers [36]. Being major components of curcumin extracts, these compounds are predictable to act against a wide-ranging number of disease-causing agents [36].

Curcumin, the main active polyphenol compound in Curcuma longa, was found to be potent in treating AITD by controlling inflammatory cytokines [30]. Some studies showed a direct association via in vitro experiments between the treatment of nontoxic concentrations of curcumin and the alleviation of inflammation in orbital fibroblast derived from Graves' patients [49]. Additionally, other studies showed curcumin to be among effective herbal medicines in the treatment of Hashimoto Thyroiditis [50]. Curcumin can interact with proteins and induce inhibitory actions. Herein, we aimed to shed light on the effect curcumin derivatives have on the protein CD14, which is a hub protein that contributes majorly to the innate immune response. Thus, in silico studies using curcumin derivatives in targeting CD14 are uncovered. Docking experiments were conducted to appreciate the plausible action mechanism by which the curcumin derivatives would inhibit the CD14 protein. Lead compounds were previously synthesized from the curcumin derivatives [36]. Screening protocols were followed that aid in checking the inhibitory potentials, binding free energies at the binding interfaces, and structural fluctuations for the ligands at the binding interfaces from the reference structures.

Previous studies concluded an inhibitory action of some flavonoids to CD14+ monocytes. An example is chrysin, a flavonoid that was found to inhibit the receptor-mediated endocytosis of CD14+ monocyte-derived immature dendritic cells [51]. This suggests an antagonistic action of chrysin on the CD14 protein, which controls the endocytosis process of toll-like receptor 4 [52]. It also attenuated the expression of CD80, CD83 and Cd86 [51]. Apigenin is another flavonoid that was also found to inhibit the expression of other clusters of differentiation, including the CD80 and CD86 [53].

Docking experiments showed good results in terms of the binding free energies, inhibition constants as well as the root mean square deviation (RMSD) values for the ligand structure upon docking from the reference structure (Table 2). In reference to literature, a scoring scheme of a binding free energy lower than -5 kcal/mol and an inhibition constant less than 100 μM indicates a strong binding between the ligand and the protein [54]. All compounds, excepting S4 and S7 showed potent binding to CD14 (PDB ID: 4GLP [13]). Indeed, the inhibition constants (Ki) for the CD14 binding interface to the S1 – S3, S5-S6 ligands were in the low range (1.19 - 10.26 μM), indicating a strong inhibition. Higher inhibition constants were found for the CD14:S4 and CD14:S7 interfaces (Ki = 234.97, 463.37 μM), what shows comparably weaker inhibition. Binding free energies of the CD14 protein to the several curcumin derivatives were in the range of (−4.55 - −8.08 Kcal/mol), indicating stable contacts. The root mean square deviations (RMSD) of the ligand crystal structures from the reference ones were

in a reasonable range from the reference structures (32-78 Å) while bindings to the several ligands, except for S4, which showed an unidentified value.

The 3D structure for the best fit results of binding for the seven ligands to the CD14 (PDB ID: 4GLP) [13] showed moderate-ranged (3.6 - 4.0 Å) electrostatic interactions, and a slight contribution for the short-ranged (2.5 - 3.5 Å) interactions at the ligand-protein interface (Figure 1). A balanced contribution of both nonpolar amino acids (e.g., Leu, Pro, Trp, Phe, Val, and Ala) as well as polar amino acids (e.g., Asn, Arg, Ser, Arg, Glu, Gln, Asn and Lys) at all binding interfaces was noticed. The only exception was the S5:CD14 interface, where the contribution was merely non-polar. These results indicate a good drug likeness for the ligands, due to their capability to bind to water and to cross biological membranes. These results were further reinforced by ADMEtox studies, especially the logP values that indicated balanced lipophilicities and hydrophilicities of the drugs. All seven ligands were also found to follow the Lipinski's RO5 and to show intermediary bioavailability scores (0.55). However, their inhibition of CYP450 suggests further needed modifications that alleviate drug-drug interactions[48].

Based on our previous work on curcumin derivatives and other phytochemicals targeted in our drug discovery protocols [22, 55, 56], the researchers predict that the phytochemical might bind several targets in different tissues, all with a high specificity. In addressing the plausible side effects of the off-target effect, nanoparticles are developed that induce an active targeting to the tissue under study, with a very high targeted localization of the drug in precision medicine. This additionally improves the toxicity profile by reducing side effects related to the unspecific binding of the phytochemicals [57, 58].

Docking is a well-established method used to understand the mechanistic insights of the protein-ligand plausible binding. However, some limitations to the performed docking study include the confined sampling for the conformational space of the protein and ligand. Additionally, the scoring schemes for the binding affinities and free energies are approximated. However, the results herein can be utilized in understanding the comparative binding affinities of the several phytochemicals to the protein under study [59, 60]. One more limitation is the limited crystallographic evidence with positive controls to serve in the validation process for the experiments held. It is necessary to handle further in vitro, in vivo and human-based research to test the clinical potential of the several phytochemicals and decipher these findings into the production of effective drugs for improving patient outcomes in treating autoimmune diseases.

5. Conclusion

It was previously suggested that the inhibition of CD14 protein can reduce the inflammatory responses [61]. Compounds derived from curcumin are robust in the treatment of a wide range of illnesses [24, 25]. This study emphasizes the mechanistic binding of compounds derived from curcumin to the CD14 protein. A special interest can be directed to the S1 – S3 and S6-S7 curcumin derivatives, which showed the best docking results. These results were based on the binding affinities, binding interfaces, and inhibition constants. Additionally, ADMEtox results and the bioavailability scores indicated good drug likeness for the several curcumin derivatives. Taken together, these in silico results serve as good basis for ongoing in vitro and in vivo studies and drug identification for the treatment of autoimmune diseases.

6. Declarations

Acknowledgments
Not applicable.

Ethical consideration
This study adhered to the principles of the Declaration of Helsinki.

Consent to participate
Not applicable

Conflicts of interest
The authors (Siba Shanak and Hilal Zaid) are members of the Editorial Board for the AAUP Journal of STEM and Health Sciences. To maintain a transparent and unbiased peer-review process, Shanak and Zaid were not involved in the selection of reviewers or any editorial decisions regarding this manuscript. The peer-review process was handled independently by other editors of the journal. Otherwise, the authors have no conflicts of interest to declare that are relevant to the content of this article.

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Data Availability
The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors Contributions
Conceptualization: Hassan Shroof and Siba Shanak. **Formal analysis**: Hassan Shroof and Siba Shanak. **Investigation**: Hassan Shroof and Siba Shanak. **Methodology**: Hassan Shroof and Siba Shanak. **Supervision**: Hilal Zaid. **Visualization**: Hilal Zaid **Writing – original draft**: Hassan Shroof and Siba Shanak. **Writing – review & editing**: Siba Shanak

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