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Molecular design and virtual screening of chlorogenic acid analogues as potential CD14 inhibitors

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Abstract: Cluster of Differentiation-14 (CD14) is a glycosylphosphatidylinositol-anchored protein that binds lipopolysaccharide (LPS) and presents it to the toll-like receptor 4 (TLR4) - myeloid differentiation factor 2 (MD-2) complex. This activity encourages the production and release of regulatory molecules, including cytokines and other inflammatory substances leading to septic shock. Septic shock syndrome is one of the leading causes of mortality in hospital intensive care units (ICUs). Currently, no single therapy has proven effective in septic shock management. One of the most prevalent naturally occurring polyphenols in plants, chlorogenic acids (CGA) have a variety of biological functions that are advantageous to human health including reducing septic shock syndrome. This study aimed to explore analogues of CGA as potential CD14 inhibitors using in silico methods. A structure-based virtual screening was carried out, using a compound library of 69 small molecules (library A) and another optimized library of 69 small molecules (library B) along with the lipid A molecule in the hydrophobic pocket on the NH_2- terminal side of the CD14 crystal structure, 1WWL.pdb. Nitrogen-containing derivatives and dicaffeoyl- substituted CGA analogues were found to have better binding affinity when compared to that of CGA and lipid A. CGA analogues were analyzed and seen not to be interacting with active site residues that are important for protecting CD14 from digestion, hence making it unavailable for LPS binding and activation. This study was able to predict potential CD14 inhibitors, which are synthesizable and can go on to be bio-assayed for immunomodulatory activities.

Keywords: CD14, lipopolysaccharide, virtual screening, septic shock syndrome, chlorogenic acid, immunomodulatory

1. Introduction

The initial line of defence against invasive germs that have breached natural physical barriers like the skin and mucosa layer is the innate immune system [1]. According to Biswas and Lopez-Collazo, it has developed to include cells and defence systems that protect the host against invading foreign organisms [2]. It is known as the acute phase defence system because it responds to antigens within hours of being triggered. The innate immune system heavily relies on the proteins Cluster of Differentiation-14 (CD14), toll-like receptor 4 (TLR4) and myeloid differentiation factor 2 (MD-2). They can distinguish between host molecules identifying them as pattern recognition receptors (PRRs), which are generally shared by pathogens, and pathogens-associated molecular patterns (PAMPs). The activation of transcription factors that support the inflammatory process and the maturation of antigen-presenting cells (APCs) occur when PAMPs are recognized by PRRs, which then transduce a signal inside the cells [3]. The innate immune response is non-specific, recognizing molecular patterns common to a wide variety of pathogens but is especially specific to the recognition of lipopolysaccharides (LPS).

The LPS is a major structural and functional component on the outer membranes of gram-negative bacteria and constitutes one of the important PAMPs. The glycosylphosphatidylinositol-anchored protein CD14 is the signalling PRR that binds the LPS and presents it to TLR4-MD-2 complex. This action promotes the synthesis and secretion of regulatory molecules such as cytokines and other pro-inflammatory chemicals such as interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor-alpha (TNF-α) and platelet activating factor (PAF). The LPS-binding activity of CD14, which is found on the surfaces of macrophages, monocytes, and neutrophils, enhances TLR-4's capacity to respond to LPS. An excessive amount of pro-inflammatory chemicals is produced when CD14 is overstimulated by LPS, which can result in organ failure, septic shock syndrome, and occasionally even death

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[4]. The global burden of sepsis and septic shock is on the increase, estimating 49 million sepsis incidence cases and 11 million sepsis-related deaths in 2017 [5]. Markwart et al., in their meta-analysis findings reported a 27 % hospital mortality rate for sepsis and a 42 % mortality rate for sepsis patients being treated in the intensive care units [6]. Most of the investigational drugs and therapeutics have done well in experimental sepsis models and animal studies with promising futures in some human studies but proved disappointing in larger-scale human clinical trials [7-10]. Peng et al., reported that mice devoid of the CD14 did not develop septic shock or accumulate pro-inflammatory cytokines when injected with LPS or exposed to *E. coli* [11].

Chlorogenic acid (CGA) is one of the polyphenolic compounds widely distributed in plants, especially in coffee, potatoes, beans and apples. CGA is a natural chemical compound that is the ester of caffeic acid and quinic acid. The term chlorogenic acids can also refer to a related family of esters of hydroxycinnamic acids (caffeic acid, ferulic acid and p-coumaric acid) with quinic acid. CGA also occurs as 3-, 4-, and 5- isomers of caffeoylquinic acids [12]; but for this study, 3-o-caffeoylquinic acid (3-CQA), shall be the focus because it is the most abundant isomer. CGA has been seen to modulate cytokine and chemokine release and suppression of immune cell apoptosis. It has also been seen to cause augmentation of bacterial elimination by attenuating the increase in toll- like receptor (TLR)-4 and suppression of sepsis-induced signaling pathway [13].

CGA and its analogues have been seen to have broad anti-inflammatory, immunomodulatory and antioxidant effects and have many intracellular molecular targets [14]. However, studies on their interactions with CD14 and if they inhibit the transmission of LPS is grossly lacking except for one study [11]. Failure to activate the TLR-4-MD-2 complex by LPS could be an interesting way to inhibit the entire TLR4 pathway to result in the reversal of pro- inflammatory chemical production and elude bacterial resistance. Being able to identify and synthesize inhibitors that are selective for CD14 would help develop therapies. On the other hand, CD14 agonists would be found to be beneficial in the selective or spontaneous initiation of immune response. CD14 could be the target of a new generation of antisepsis agents.

This study was designed to use in silico methods to design, optimize and virtually screen for CD14 inhibitors using chlorogenic acid as a lead.

2. Experimental

This docking study employed a variety of web interfaces, online databanks and software programs; all procedures were entirely conducted *in silico*.

2.1 Library design of small molecules and molecular target

A library of 69 small molecules was built by including molecules from a similarity and substructure search on PubChem [15] using the 2D structure of CGA. The molecules were filtered to retain molecules that were drug-like and fit the Lipinski's rule of five. Hydrophobic molecules were chosen by adjusting the LogP filter to be between 1-5. 3D coordinates of these molecules were downloaded, and their valences and hybridizations were checked in BIOVIA Discovery Studio Visualizer 4.5 [16]. This library was labeled as library A. A second library was designed by optimization of CID_25016602; which was the best ligand from compound library A using SwissBioisostere's fragment replacement feature [17, 18]. This generated 69 small molecules which were included in another library labeled library B [Table 1]. The natural ligand used in this study was the Lipid A portion of the LPS molecule. Lipid A structure was drawn in Scigress Workspace [19] and Molecular Mechanics geometry optimization performed on it.

The 3D crystal structure of CD14; 1WWL downloaded from the protein databank (http://RCSB.org) [20]. The structure 1WWL.pdb was opened in [16] and all water molecules and bound ligands deleted. MolProbity Ramachandran Plot Analysis webserver was used to run a Ramachandran plot analysis on the 3D crystal structure of CD14 (1WWL) [21].

2.2 Docking studies

Docking studies were performed using small molecules in the libraries against the 3D crystal structure of CD14. Ligands and protein target for molecular docking were prepared in Autodock tools using PyRx 0.8 package [22]. A grid box (x: 25.9842, y: 44.9959, z: -7.1500), dimensions (A): X:49.7475, Y: 38.7156, Z: 56.0035 was employed and docking simulations of bioactive conformations was done using Autodock Vina [23]. The gridbox covered the active site in CD14 structure including residues in the hydrophobic pocket and rim of the NH-terminal. These residues include ASP11-SER14, PRO22- ASP25, ALA35-GLU39, and GLU57- PHE63, which correlated to regions 1, 2, 3 and 4 [24]. The ligands were inputted as sdf files while the target protein was inputted as a pdb file then converted to the acceptable pdbqt file format for Autodock Vina. Results obtained from docking studies were analyzed using PyMol [25] and Discovery Studio 4.5 visualizer [16].

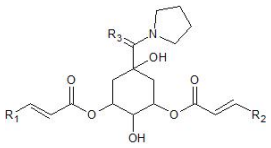
3. Results and discussion

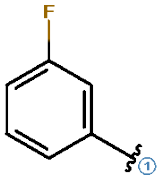
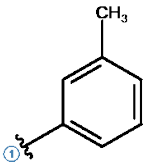
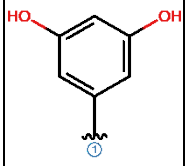
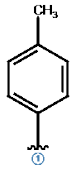
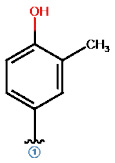
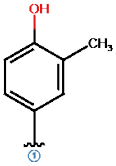
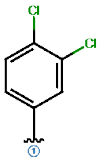
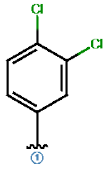
3.1 Lead optimization

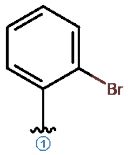
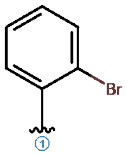
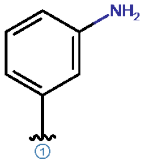
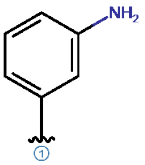
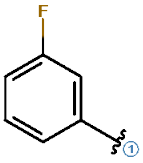
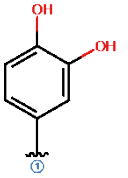
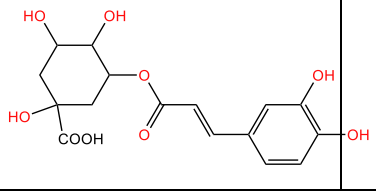
It is very practical to reliably rule out bad designs early in the drug development process since the diversity of chemical entities that can be synthesized seems to be infinite, and most of these compounds seem to be

uninteresting from a pharmaceutical standpoint [26, 27]. As lead optimization progresses, properties like toxicity and bioavailability are now getting more consideration in addition to potency gains. In keeping with this plan, computational chemistry becomes more and more crucial to tackling these problems [28]. To forecast physical, chemical, and biological properties that are pertinent to *in vivo* efficacy and therapeutic medication safety, a substantial number of resources are currently devoted to the creation and use of *in silico* ADME and toxicity models [29]. Bioisosteric replacement is an efficient way of optimizing a series of molecules by replacing a moiety on the compound with another; hereby creating a new molecule with similar biological properties to the parent compound [18]. Bioisosteric replacements, represented in table 1, were influenced by the medicinal alerts on the catechol rings in CID-25016602, by removing substructures that might be a source of false-positives in the drug discovery process [30].

Table 1. Bioisosteric replacement of the catechol rings in CID-25016602 for the design of compound library B and their corresponding binding energies (Kcal/mol) to CD14 (1WWL).



MOLECULE	R1	R2	R3	Binding Energy (Kcal/Mol)	H-bond interaction	Hydrophobic interaction
(**CGA-OP18**) 2,5-dihydroxy-5-(pyrolidine-1-carbonyl)-3-(((E)-3-(m-tolyl)-acryloyl)-oxy)-cyclohexyl (E)-3-(3-fluorophenyl)-acrylate				-10.1	Arg45, Gly42	Ala29, Ala90 Leu47, Leu70, Leu75, Leu102, Leu104, Phe 19, Phe30, Val77
(**CGA-OP23**) 2,5-dihydroxy-5-(pyrolidine-1-carbonyl)-3-(((E)-3-(p-tolyl)-acryloyl)-oxy)-cyclohexyl-(E)-3-(3,5-dihydroxyphenyl)-acrylate				- 9.5		Ala 80, Leu40, Leu47, Leu50, Leu50, Leu 72, Phe19, Tyr49, Val38
(**CGA-OP39**) 2,5-dihydroxy-5-(hydroxy-(pyrolidine-1-yl)-methyl)-cyclohexane-1,3-diyl-(2E,2'E)-bis(3-(4-hydroxy-3-methylphenyl)-acrylate				- 9.5	Ala58, Ile 86	Leu40, Leu47, Leu70, Leu72, Phe19, Val: 38, Val54, Val 93
(**CGA-OP24**) 2,5-dihydroxy-5-(pyrrolidine-1-carbonyl)-cyclohexane-1,3-diyl-(2E, 2'E)-bis(3-(4-				- 9.4		Ala90, Ile66, Ile67, Ile82, Leu 87, Leu50, Leu102, Leu104, Leu107, Phe30, Phe63, Trp 26, Tyr49

dichlorophenyl)-acrylate						
(**CGA-OP32**) 2,5-dihydroxy-5-(pyrrolidine-1-carbonyl)-cyclohexane-1,3-diyl-(2E, 2'E)-bis(3-(2-bromophenyl)-acrylate				- 9.2		Ala29, Leu 40, Leu 47, Leu 70, Phe 30, Phe63
(CGA-OP15) 2,5-dihydroxy-5-(hydroy-(pyrrolidine-1-yl)-methyl)-cyclohexane-1,3-diyl-(2E, 2'E)-bis(3-(3-aminophenyl)-acrylate				- 9.1	Ala29, Phe19	Ala58, Ala80, Ala90, Leu40, Leu47, Leu70, Leu 72, Val54, Val58
(CGA-OP19) 3-(((E)-3-(3,4-dihydroxyphenyl)-acryloyl)-oxy)-2,5-dihydroxy-5-(hydroxy-(pyrrolidin-1-yl)-methyl)-cyclohexyl-(E)-3-(3-fluorophenyl)-acrylate				- 8.6	Asp55, Phe 30	Ala29, Ala58, Cys32, Leu40, Leu70, Leu72, Phe19, Val38, Val 54, Val93
(CGA) 3- caffeoylquinic acid				-6.6	Asp55, Leu55	Ile86, Ile 40

Ala- Alanine, Asp- Aspartic acid, Arg- Arginine, Cys- Cysteine, Gly- Glycine, Ile- Isoleucine, Leu- Leucine, Trp- Tryptophan, Tyr- Tyrosine, Val- Valine

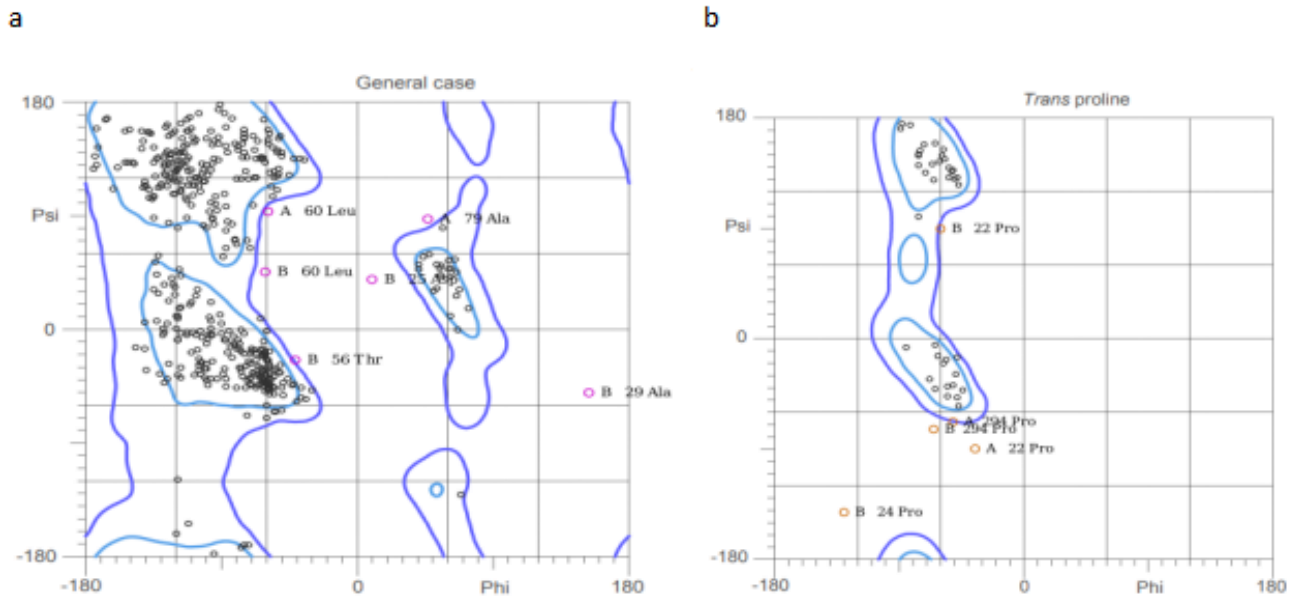


Figure 1. Ramachandran plot of the 3D crystal structure of CD14 (1WWL). Pink dots in the General case (a) and orange dots in the trans-proline (b) plot represent amino acid residues in the disallowed regions, while black dots represent amino acid residues in favoured and allowed regions [21, 31].

3.2 Predicting binding affinity from docking score and binding pattern

Ligand orientations are ranked in relation to other poses and ligands in the compound library and scored in relation to intermolecular energy interaction. Molecule alignment provides evidence for a shared binding mechanism, particularly when the structure activity relationship (SAR) of related molecular components exhibits parallel trends [32]. The replacement of the carbonyl-OH group on the quinic acid moiety with a nitrogen containing functional group on the analogues designed from CGA showed a significant decrease in predicted binding energy. Analogues from library B (CGA-OP18; -10.1 Kcal) were seen to have higher binding energies than analogues from library A (CID-25016602; -11.0 Kcal). This is not an issue seeing that compounds in library B were an optimization from the best ligand from compound library A.

Substrates, as well as small molecules interacting with enzymes and protein active sites, exhibit interactions including covalent and non-covalent bonding; ionic, hydrogen, and van der Waals interactions. For biological processes like protein-ligand recognition, these interactions are crucial. The protein-ligand connection must be strong enough to keep the ligand in the binding site and prevent it from leaving before any sensible response between the two can occur. Additionally, the reaction product should be released by a weak enough contact. Consequently, an inhibitor that can bind to the active site more firmly than the natural substrate and cause blockage and restricted access to the active site would be significant [33]. Ramachandran plots of the 3D crystal structure of CD14 confirmed the good quality of the protein target for this study. The MolProbity Ramachandran plot showed the residues in the different regions according to phi and psi angles [31]. 89.6% (552 of 616) of all residues were in favored regions, while 98.2 % (605 of 616) of all residues were in allowed regions with 11 of the residues as outliers (Figure 1).

From this study, it was observed that interactions of the small molecules to the CD14 active site were generally through (van der Waals contact) hydrophobic interactions, while some of the small molecules were also shown to be involved in pi-pi interactions (Figure 2). Leucine-rich repeats have been proposed to facilitate protein-lipid interactions [34]. Leucines 87, 91 and 94, in addition to

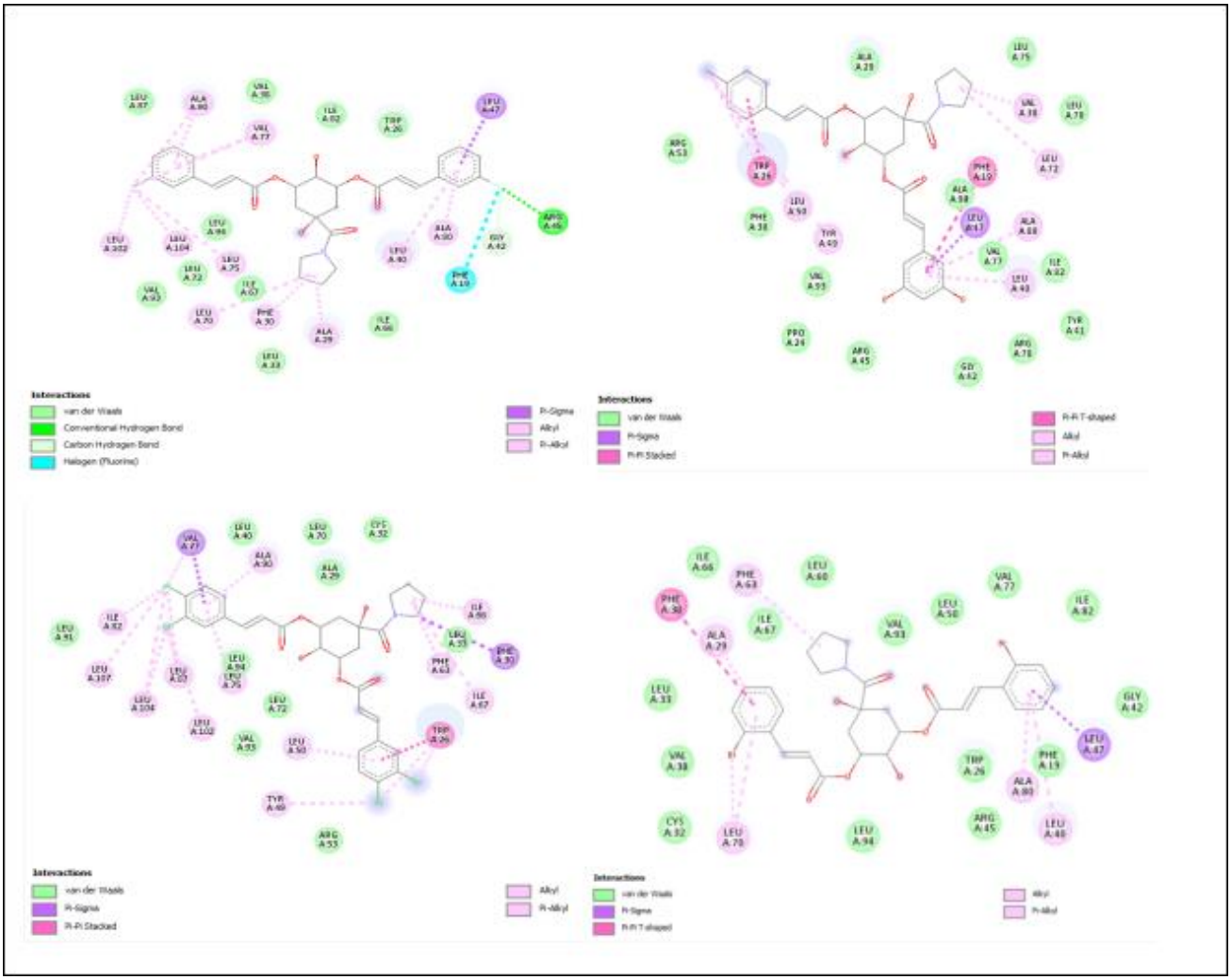


Figure 2. Binding interactions of (a) CGA-OP18, (b) CGA-OP23, (c) CGA-OP24, and (d) CGA-OP32 to the binding site of 1WWL (CD14). Ligands are shown in stick forms while amino acid residues are shown in disc forms.

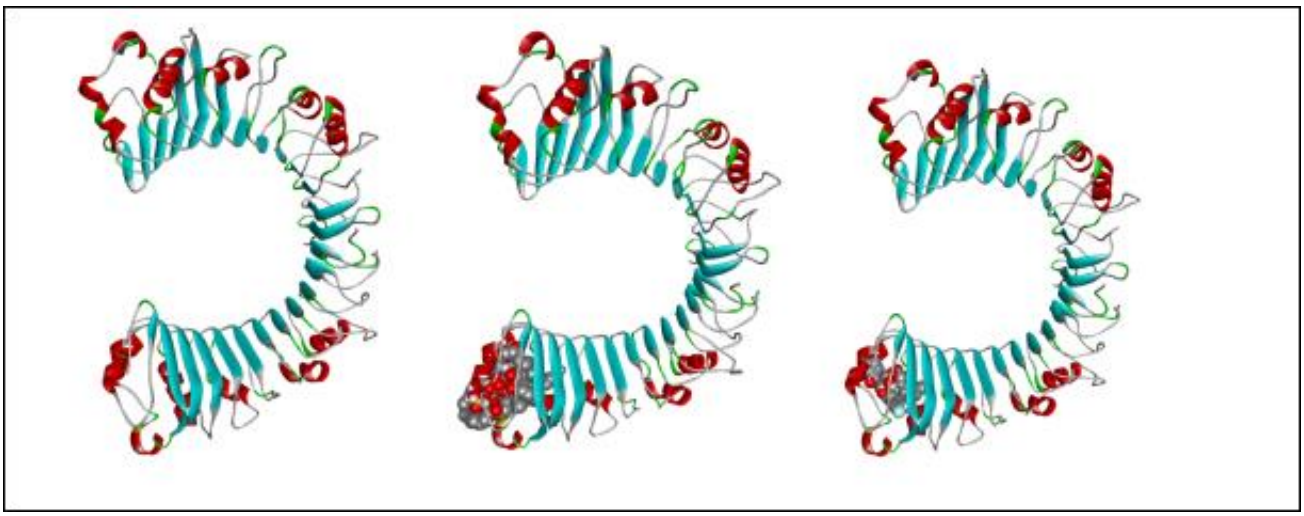


Figure 3. Ribbon representation of the CD14 dimer structure (a) unbounded, (b) CD14- LPS complex, and (c) CD14- CGA-OP18 complex. Ligands are in coloured spheres, showing no global structural changes in CD14 (1WWL).

LPS-binding activity have been revealed to also have a strong LPS neutralising activity [34]. All small molecules were seen to interact with residues from all over the NH_2-terminal pocket sub-pocket, rim, wall and base [24] of the CD14 protein. This supports the hypothesis proposed by Cunningham et al. that the CD14 protein, to interact with various ligands, presents numerous charged residues located throughout the NH_2- terminal pocket to participate in ligand binding [35]. In addition, CD14 also offers a range of different potential binding interactions to its numerous ligands by orientating several of its groups of NH_2- terminal residues. Residues Arg45, Tyr49 and Leu87 have been proposed to create additional hydrophobic interactions to stabilize the complex [36]; several CGA analogues from this study were seen to have interacted with these residues (Figure 3). Also, interactions of LPS with CD14 residues

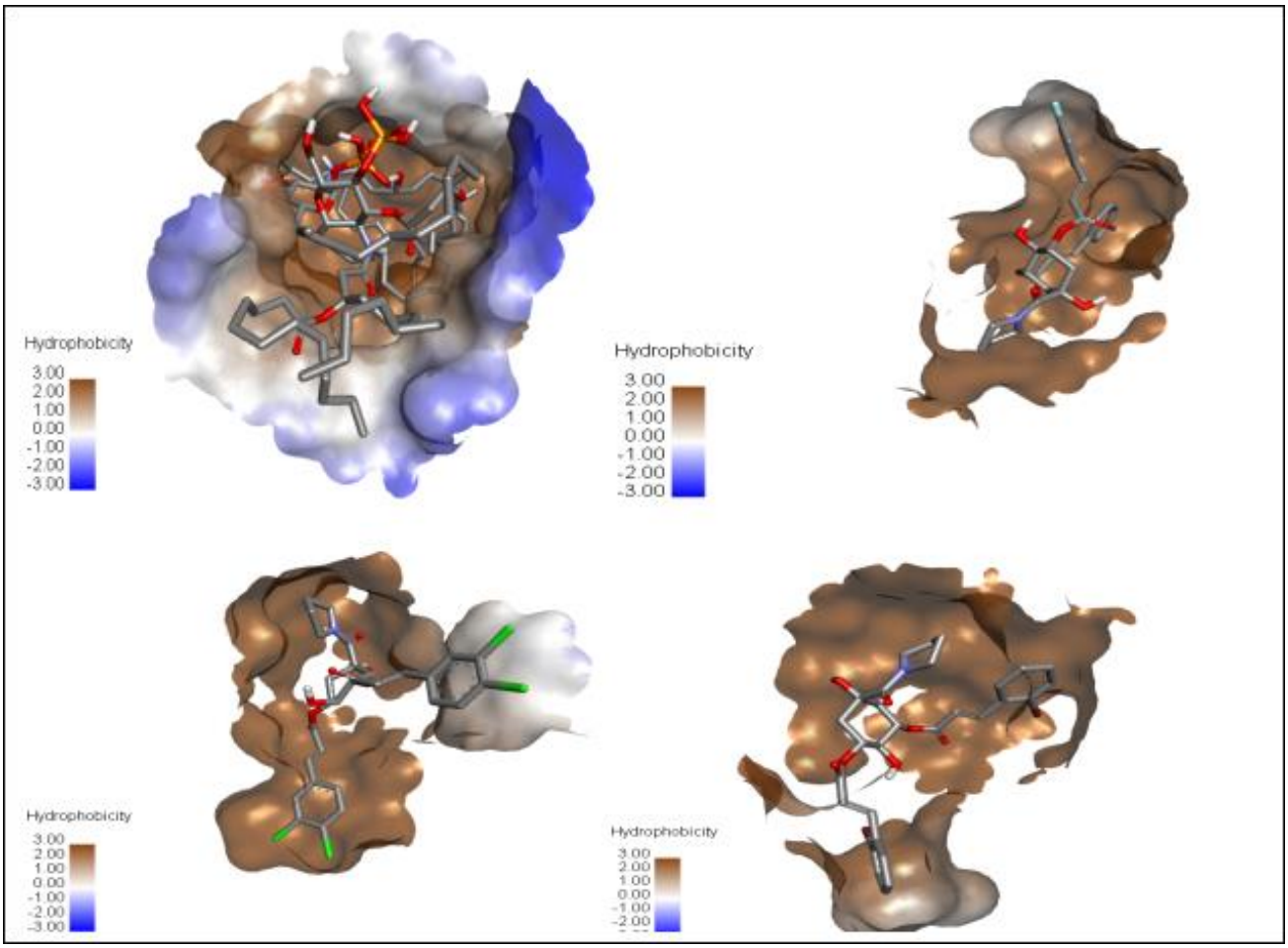


Figure 4. Dock poses of (a) lipid A; (b) CGA-OP18; (c) CGA-OP24 and (d) CGA-OP32, to the binding site of 1WWL (CD14). Ligands are shown in stick forms while hydrophobic regions in the binding pocket are colored brown.

57-64 have been seen to limit the action of endoprotease AspN [37], observation of the small molecules in this study showed minimal interactions with the said residues. This can be assumed that the occupation of the CD14 binding site by the predicted small molecules in this study leaves it vulnerable to be digested; hence it will no longer be available for LPS binding.

3.3 Implication of small molecule binding and occupation of binding site on CD14 mechanism

All the small molecules used in this study were observed to have docked properly in the active site. Upon binding of the small molecules to CD14, no global structural changes were observed. Local structural changes can be observed in the CD14 within the α2 and α3 helices and their connecting loops (Figure 4). The connecting loop between the α2 and α3 helices includes amino acids between 57- 64, which are included in region 4 as described by Kim et al. [24]. When compared to unbounded CD14, a significant change in the loop connecting α2 and α3 helices was observed upon LPS and ligand binding to CD14 active site. It is thought that hydrophobic residues rearrange upon binding to LPS and acylated ligands to accommodate them [35]. The dock pose of a ligand in the protein active site helps to give an insight into the ligand's ability to occupy the active site or how well it is occupying it. CD14 binding to LPS is in a stoichiometric fashion; 1 or 2 monomeric molecules of LPS bind to CD14 [38]. Therefore, it can be proposed that, if a small molecule interacts with CD14, by occupying all or part of the active site as seen in this study (Figure 4), CD14 would be unavailable to LPS molecules.

4. Conclusion

Small compounds with a potential affinity for the CD14 receptor were predicted by virtual screening, docking investigations, and *in silico* molecular design. Since prior research has shown that chlorogenic acid has promising potential as an immunomodulatory drug, it was chosen as the lead to create a series of candidate compounds for input into the docking investigations. When compared to CGA and lipid A, analogues with nitrogen-containing derivatives and dicaffeoyl-substituted CGA analogues were predicted to have a higher binding affinity. It was shown that these small molecules interacted with the residues necessary for LPS binding and signaling. However, it should be highlighted that ranking and docking score results do not prove anything in themselves. Consequently, even though this analysis cannot be used to forecast "potential ligands", it helps to identify leads that could be helpful as starting points. Potential ligands can only be confirmed by synthesizing and testing these molecules, as this study only point in what direction to go. The molecules found to be highly ranked could be optimized and subjected to further investigations.

Declarations

Author Contribution: OCP, UA and TEA developed the concepts for the ideas presented in the article; OCP did the literature search, molecular docking and first draft of the original manuscript; UA and TEA reviewed the manuscript and supervised the project.

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Conflict of Interest: Authors declare no conflict of interest.

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