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Research Article

MOLECULAR DOCKING OF SOYA PHOSPHATIDYLCHOLINE (SOYA PC) WITH VARIOUS INFLAMMATORY MEDIATORS (CYTOKINES): AN *IN SILICO* STUDY

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ABSTRACT

Soya Phosphatidylcholine (PC) is commonly referred to as soya lecithin. Lecithin is widely used as a drug carrier in the form of liposomes. Additionally, the soya PC also has suggested a potential role in the management of various inflammatory diseases. The inflammatory response is almost common in many diseases, exaggerated by the persistent infiltration of various inflammatory cells and the release of proinflammatory mediators. Toll-like receptor 4 (TLR4) plays a key role in amplifying inflammatory response by releasing various proinflammatory cytokines. The literature has suggested the TLR4 antagonistic potential of soya PC. However, the potential effect of soya PC on proinflammatory cytokines is still hidden. Thus, with the renewed interest, the present study was undertaken to investigate the molecular binding of three different soya PC based on their fatty chain variation against various proinflammatory cytokines (IL-1β, IL-6, and TNF-α) using *in silico* computational docking. The structures were retrieved from the protein databank and PubChem. The molecular docking study was performed using the Autodock software, and bond interactions were analyzed using Discovery Studio 4.1 Visualizer. The results suggested all three ligands showed good binding affinity towards the selected protein receptors. However, Soya PC (16(0)16(0)) showed best docking score compared to PC (16(0)18(2)) and PC (18(2)18(2)).

Keywords: Molecular Docking, Soya Phosphatidylcholine, TLR4, IL-1β, IL-6, TNF-α, Inflammation.

1. INTRODUCTION

Inflammatory abnormalities are a major group of disorders underlining a wide variety of diseases in humans. The inflammatory response is mediated through various inflammatory cells (leukocytes, macrophages, dendritic cells, and mast cells) and inflammatory mediators (cytokines and chemokines) [1]. TLRs (Toll-like receptors) are pattern recognition receptors (PRR) that selectively recognize various pathogen-associated molecular patterns (PAMPs) shared by microbes or danger-associated molecular patterns (DAMPs), the endogenous molecules produced from the injured/stressed cells, thereby contributing innate and adaptive immune responses. Signaling of TLR4 receptor by PAMPs or DAMPs results in the initiation of NF-κB, which triggers the gene expression for many proinflammatory cytokines [2-3]. The released proinflammatory cytokines have a negative effect.

Cytokines are small soluble proteins produced from inflammatory cells that may have a pleiotropic effect and are redundant in the activity. They are frequently produced in the cascade [4]. Cytokines regulate the host responses to infection, immunity, inflammation, and traumatic events. Some cytokines can worsen the disease, termed as proinflammatory cytokines (IL-1, IL-6, and TNF-α), While others serve to decrease inflammation and promote healing, termed as anti-inflammatory cytokines (IL-10) [5]. Proinflammatory cytokines promote systemic inflammation through the upregulation of inflammatory reactions. In contrast, anti-inflammatory cytokines control the proinflammatory cytokine responses through immunoregulatory molecules. In normal conditions, the responses are well-regulated. However, in some diseased conditions, the proinflammatory cytokines are needed to be controlled.

Toll-like receptors 4 (TLR4) and released proinflammatory cytokines, IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), or type 1 interferon (IFNs) [6-8] have suggested predominant role in the underlying

pathogenesis of diseases like vasculitis, arthritis, asthma, ulcerative colitis, autoimmune diseases, metabolic diseases.

Soya Phosphatidylcholine has suggested potential benefits in various inflammatory diseases such as arthritis [9], ulcerative colitis [10], and cancer [11]. In our previous computational study, we determined the binding activity of three different soya Phosphatidylcholine (PC) with TLR4-MD2 complex. The docking result showed the highest binding affinity of Soya PC with TLR4-MD2 receptor complex compared to LPS (specific TLR4 agonist), and Eritoran (TLR4 antagonist) molecule. However, the variation was found in the binding pocket to TLR4-MD due to the difference soya PC fatty acid chain compositions [12]. The Soya PC tends to bind with the TLR4 receptor. However, its binding activity on TLR4 underlying signaling molecules are still unknown. Thus, with the renewed interest and to reveal the binding activity of Soya PC on proinflammatory cytokines. We aimed to study the Soya PC's *in silico* interactions with the selected proinflammatory cytokines.

2. MATERIAL AND METHODS

2.1. Software

AutoDock 4.2 software was downloaded from www.scripps.edu and Discovery Studio Visualizer 4.1 was downloaded from www.accelerys.com

2.2. Docking studies:

2.2.1. Proteins Preparation

The three dimensional crystal structures of proinflammatory cytokines (proteins) IL-1β, IL-6 and TNF-α (PDB ID- 4G6J, 1N26 and 2AZ5, respectively) were retrieved from the protein databank (www.rcsb.org/pdb). Protein was prepared by using Discovery Studio 4.1 Visualizer. The water molecule and all the heteroatoms were removed from the protein molecules. Polar hydrogen atoms were added for partial charge computation. The grid was defined and the selected macromolecules were converted into their corresponding pdbqt formats.

2.2.2. Ligands preparation

Soya phosphatidylcholine with three different fatty acid chain conformations (16(0)16(0), 16(0)18(2), and 18(2)18(2)) were selected and downloaded from PubChem in pdb format. The optimization of ligands were done using the Autodock tool and saved as pdbqt format.

2.2.3. Protein-Ligand Molecular Docking

The protein-ligand binding activity was assessed using Autodock software. The Lamarckian genetic algorithm was applied for energy minimization using default parameters. The binding affinity was determined on the basis minimum binding energy of receptor bound ligands and number of hydrogen bond. The docking results were visualized by Discovery Studio 4.1 Visualizer.

3. RESULTS AND DISCUSSION

We are the first to demonstrate the binding activity of Soya PC with proinflammatory cytokines. In the present *in silico* study, the molecular docking was performed on the active sites of 4G6J, 1N26 and 2AZ5 (IL-1β, Il-6, and TNF-α, respectively) against soya PC with three different fatty acid chain conformations (PC (16(0)16(0)), PC (16(0)18(2)), and PC (18(2)18(2)) individually. All the ligands were successfully docked on the active sites and were found stable due to the hydrogen bond formation. The best binding ligand was selected, having the lowest binding energy and a high hydrogen bond formation. The docking interactions between soya PC and the selected cytokines has been presented in Figure. 1-3. The binding energy of the interactions and hydrogen bond formation has been listed in Table 1-3.

Table 1: Binding energy and hydrogen bonds of preferably docked conformation (presented in Figure 1A-C) of soya phosphatidylcholine (PC 16(0)16(0), PC 16(0)18(2) and PC 18(2)18(2)), on 4G6J (crystal structure of IL-1β) using Autodock software

Sr. No.	IL-1β	Binding Energy (k cal/mol)	No. of Hydrogen bonds	Residues involved in hydrogen bonding
1.	Soya PC (16(0)16(0))	42.5	3	UNK0:C::L:SER43:O UNK0:C::H:GLN110:O L:ASP41:O::UNK0
2.	Soya PC (16(0)18(2))	59.7	2	UNK0:C::H:GLY109:O UNK0:C::UNK0:O
3.	Soya PC (18(2)18(2))	78.1	2	UNK0:C::H:TRP108:O UNK0:C::UNK0:O

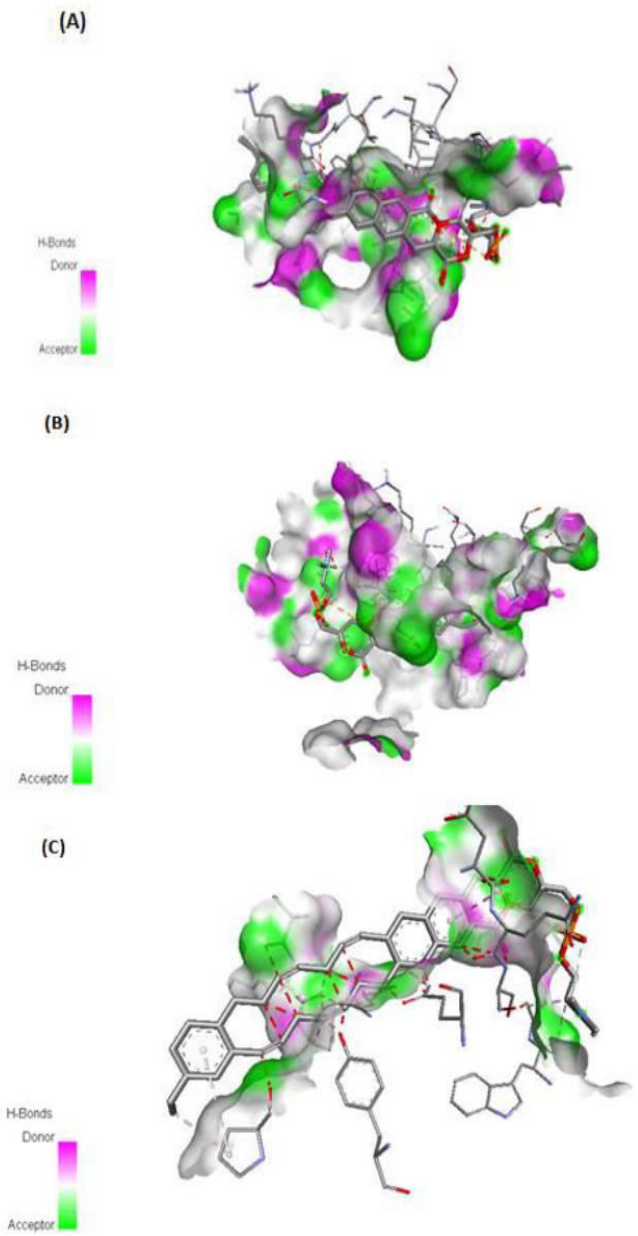

Fig. 1: Docking interactions and binding characteristics of soya phosphatidylcholine with IL-1β. (A) binding characteristics of PC (16(0)16(0)), (B) binding characteristics of PC (16(0)18(2)) and (C) binding characteristics of PC (18(2)18(2)) on IL-1β (PDB No. 4G6J), respectively.

Soya PC (16(0)16(0)) was bound well by forming 3, 3, and 2 hydrogen bonds to the protein receptors (4G6J, 1N26, and 2AZ5, respectively) with the recorded binding energies of 42.5 kcal/mol against 4G6J, -4.2 kcal/mol against 1N26, and -9.3 kcal/mol against 2AZ5. (Fig. 1A-3A) (Table 1-3).

Soya PC (16(0)18(2)) formed 2, 4, and 4 hydrogen bonds with the recorded lowest binding energies of 59.7 kcal/mol against 4G6J, -3.5 kcal/mol against 1N26, and -8.2 kcal/mol against 2AZ5. (Figure 1B-3B) (Table 1-3).

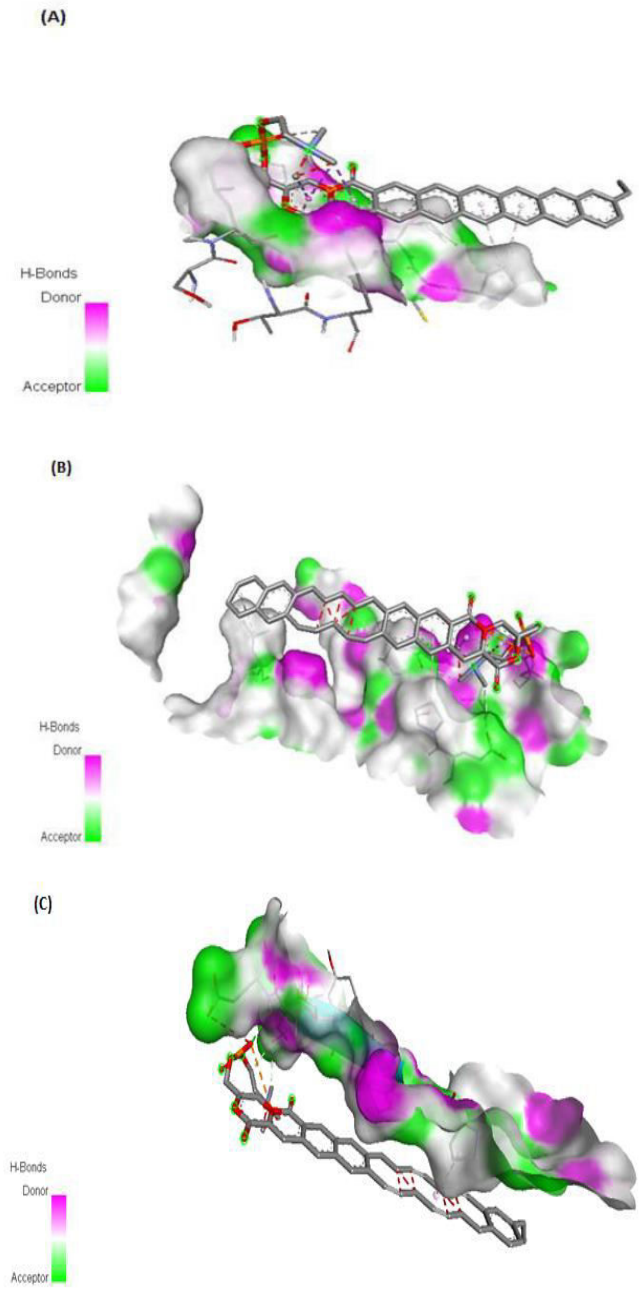

Fig. 2: Docking interactions and binding characteristics of soya phosphatidylcholine with IL-6. (A) binding characteristics of PC (16(0)16(0)), (B) binding characteristics of PC (16(0)18(2)) and (C) binding characteristics of PC (18(2)18(2)) on IL-6 (PDB No. 1N26), respectively

Similarly, Soya PC (18(2)18(2)) showed binding affinity by forming 2, 3, and 2 hydrogen bonds with the recorded lowest binding energy of 78.1 kcal/mol against 4G6J, -3.1 kcal/mol against 1N26, and -7.1 kcal/mol against 2AZ5. (Fig. 1C-3C) (Table 1-3).

The docking of the ligands with the selected protein receptors showed variations in the binding affinity due to their fatty chain differences. However, the binding affinity of Soya PC (16(0)16(0)) was found higher compared to the PC (16(0)18(2)) and PC (18(2)18(2)) due its lowest binding energy. The relative binding affinity of all three docked ligands has been indicated below.

PC (18(2)18(2)) < PC (16(0)18(2)) < PC (16(0)16(0)

Conversely, considering the receptor specificity, Soya PC's affinity is higher for TNF-α compared to IL-1β and IL-6. The relative binding affinity of ligands to receptor proteins has been indicated below.

IL-1β < IL-6 <TNF-α

Toll-like receptors 4 (TLR4) and inflammatory cytokines (IL-1β, IL-6, and TNF-α) have been key mediators in autoimmune diseases. Activation of TLR4 signaling amplifies inflammatory response through the initiation of NF-κB, which initiates the release of various pro-inflammatory mediators, including IL-1β, IL-6, and TNF-α [13-14]. The proinflammatory cytokines (IL-1β, IL-6, and TNF-α) are of interest as therapeutic targets in several autoimmune diseases. Many IL-1β, IL-6, and TNF-α neutralizing agents have been successful approved due to their clinical significance. In the present study, an attempt to determine the binding activity of soya PC directed to the selected cytokines has been analyzed. Here we report the potential binding affinity and energy of soya PC against the selected proinflammatory cytokines that may compromise the underlying signaling process of IL-1β, IL-6, and TNF-α. This further indicates the possibility of their inhibitory functions in the in-vitro and in-vivo studies.

Table 2: Binding energy and hydrogen bonds of preferably docked conformation (presented in Figure 2A-C) of soya phosphatidylcholine (PC 16(0)16(0), PC 16(0)18(2) and PC 18(2)18(2)), on 1N26 (crystal structure of IL-6) using Autodock software

Sr. No.	IL-6	Binding Energy (k cal/mol)	No. of Hydrogen bonds	Residues involved in hydrogen bonding
1.	Soya PC (16(0)16(0))	-4.2	3	A:LYS126:HZ2::UNK0:O UNK0:C::UNK0:O A:TYR148:HN::UNK0
2.	Soya PC (16(0)18(2))	-3.5	4	A:ASN110:HD22::UNK0:O UNK0:C::A:GLU144:OE1 UNK0:C::A:GLN158:O UNK0:C::A:GLN147:OE1
3.	Soya PC (18(2)18(2))	-3.1	3	A:GLU151:HN::UNK0:O UNK0:C::A:GLN150:OE1 UNK0:C::A:GLN150:OE1

Table 3: Binding energy and hydrogen bonds of preferably docked conformation (presented in Figure 3A-C) of soya phosphatidylcholine (PC 16(0)16(0), PC 16(0)18(2), and PC 18(2)18(2)), on 2AZ5 (crystal structure of TNF-α using Autodock software.

Sr. No.	TNF-α	Binding Energy (k cal/mol)	No. of Hydrogen bonds	Residues involved in hydrogen bonding
1.	Soya PC (16(0)16(0))	-9.3	2	UNK0:C::D:LEU120:O UNK0:C::UNK0:O
2.	Soya PC (16(0)18(2))	-8.2	4	B:LYS11:HZ1::UNK0:O B:LYS11:HZ3::UNK0:O B:LEU157:HT::UNK0:O UNK0:C::B:ALA156:O
3.	Soya PC (18(2)18(2))	-7.1	2	B:LEU157:HT: :UNK0:O UNK0:C::UNK0:O

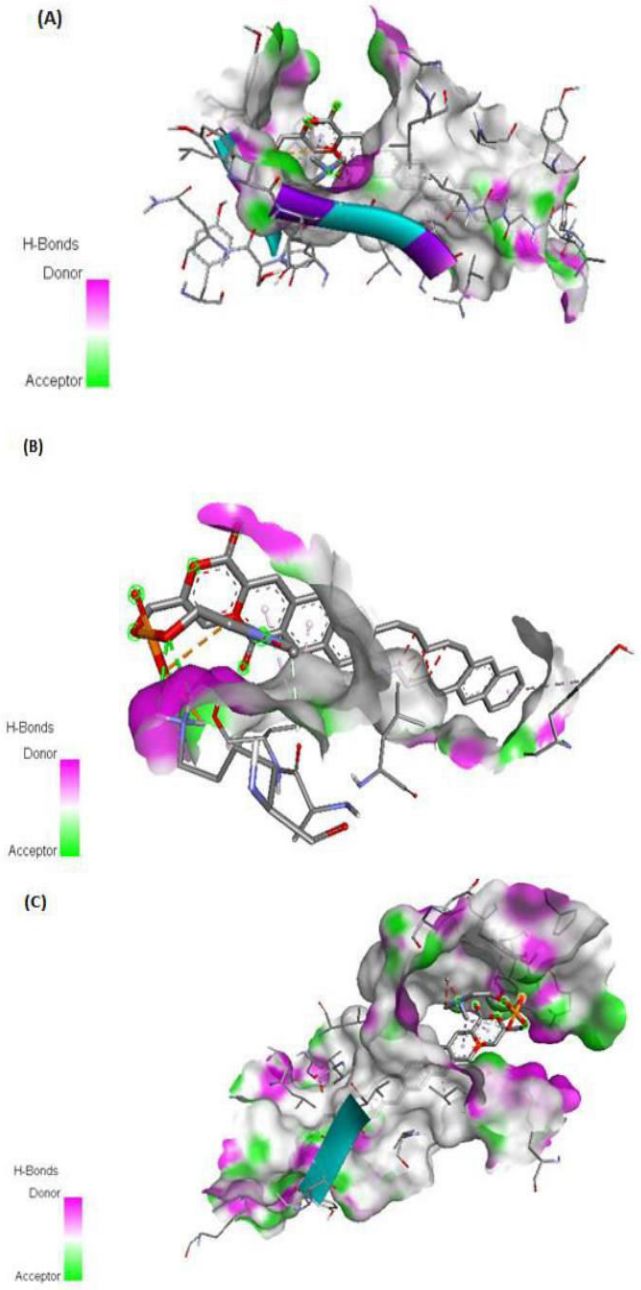

Fig. 3: Docking interactions and binding characteristics of soya phosphatidylcholine with TNF-α. (A) binding characteristics of PC (16(0)16(0)), (B) binding characteristics of PC (16(0)18(2)) and (C) binding characteristics of PC (18(2)18(2)) on TNF-α (PDB No. 2AZ5), respectively

4. CONCLUSION

The results of this study demonstrate a notable interaction between the Soya PC's and the selected proinflammatory cytokines. Soya PC (16(0)16(0)) has shown highest binding affinity compared to PC (16(0)16(2)) and PC (18(2)18(2)). This study adds a new finding that Soya Phosphatidylcholine can modulate the underlying signaling process by inhibiting the inflammatory cytokines.

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