Targeting IL-17 AND IL-17D receptors of rheumatoid arthritis using phytocompounds: A Molecular Docking study

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Targeting IL-17 AND IL-17D receptors of rheumatoid arthritis using phytocompounds: A Molecular Docking study

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune condition of the connective tissue in synovial joints, characterized by inflammation which can lead to bone and cartilage destruction. IL-17 and IL-17D cytokines produced by a number of cell types, primarily promote pro-inflammatory immune responses and negative regulator in fibroblast growth factor signalling. Thus, the promising therapeutic strategies focus on targeting these cytokines, which has led to the identification of effective inhibitors. However, several studies focused on identifying the anti-arthritic potential of natural compounds. Therefore, in the present study we undertook in silico investigations to decipher the anti-inflammatory prospective of phytocompounds by targeting IL-17 and IL-17D cytokines using Patch Dock algorithm. Additionally, IL-17 and IL-17D proteins structure were modelled and validated for molecular docking study. Further, phytocompounds based on anti-inflammatory property were subjected to Lipinski filter and ADMET properties indicated that all of these compounds showed desirable drug-like criteria. The outcome of this investigation sheds light on the anti-inflammatory mechanism of phytocompounds by targeting IL-17 and IL-D for effective treatment of RA.

1. Introduction

Rheumatoid arthritis (RA), a chronic inflammatory autoimmune disease of which etiology is unknown, leads to aggressive inflammation in the synovial joints, resulting in consequent cartilage destruction and bone erosion, which further causes severe disability as well as increased mortality rates [1], [2]. This disease affects largely women more than men detoriating the quality of health, increasing complications and early mortality in patients. Several conventional treatment methods of RA includes early diagnosis if possible and intensive treatment involving DMARD (methotrexate, leflunomide, hydroxychloroquine), NSAIDs, steroids, and biologic agents, however the disadvantage of such treatment not completely cured the disease progression [3].

Simultaneously, other biological targets involving components of immune system involved in the disease establishment that can be blocked to treat the disease. One such biological class targeted are TNF – tumor necrosis factor and Interleukin 6 receptor (IL-6 receptor). Agents targeting IL-6 receptor and TNF blockers along with DMARD are approved to be used in treatment of RA [4]. However, in both the percentage of patients showing prolonged and very less treatment response, approximately 30-40 %. Hence, there is a growing need to search for novel biological targets that overcome the

drawbacks of conventional treatment methods currently used for RA treatment [4], [5]. A large group of cytokines called as Interleukins (ILs) have been known to play a crucial role in the pathogenesis of RA by inducing various immune responses such as inflammation and causing alteration in cell behaviour [6]. IL-17 and IL-17D, group of pro-inflammatory cytokines member in IL-17 family. There have been many scientific studies reporting the prominent role of IL-17 and IL-17D in human RA and other inflammatory autoimmune diseases [7]. The research investigations showed that the elevated levels of IL-17 in serum of many RA patients. Over-expression of IL-17 by rheumatoid synovial tissue in animal models has led to degradation of bone and cartilage [8]. IL-17 and IL-17D play a key role in the disease pathogenesis by inducing inflammation in synovial tissue and by recruiting neutrophils and monocytes, secretion of other cytokines in turn adding onto the inflammation and affecting the bone metabolism. Hence, based on previous scientific evidences provided by various studies in role of IL-17 and IL-17D in RA, it can be concluded that overexpression of IL-17 and IL-17D are bone destructive cytokines [9], [10] and can be used as potential therapeutic targets in RA that can overcome the drawbacks of current treatment strategies. Consequently, biologics are quite effective in controlling the progression of the disease. However, their persistent practice is associated with severe adverse reactions including sever infections. Additionally, these conventional drugs particularly biologics are very expensive as well as it is very difficult for many patients in the developing countries to manage them. Therefore, there is unremitting search for relatively less expensive yet efficient alternatives to conventional drugs for the treatment. In this context, natural plant products comprise with vigorous and optimistic resource for identifying novel therapeutic agents for RA that meet these standards.

Plant products have been the source of a huge number of bioactive compounds with therapeutic prospective of which various eventually have been established into drugs that are consumed globally for diverse disorders including autoimmune diseases, infectious diseases, and cancer [11], [12], [13]. Furthermore, a range of herbal products belonging to the various traditional systems of medicine are either already being used by autoimmune diseases patients including RA (with or without physicians knowledge) or are under investigation for their efficient therapeutic potential [14], [15]. In the present study, we investigated the mechanism of IL-17/IL-17D with anti-inflammatory phytocompounds to determine their potential in the management of RA.

2. Materials and methods

2.1. 3D structure modelling

The amino acid sequences of human IL-17 and IL-17D was retrieved from Uniprot database. The Fasta sequences subjected to BLAST against PDB database to identify template protein structure. Lack of full length template protein we were generated IL-17 and IL-17D protein structure using abinitio modelling with I-TASSER (Iterative Threading Assembly Refinement) on-line server by iterative structural fragment reassembly [16]. Validations of the modeled proteins were carried out with PROCHECK using Ramachandran plot [17].

2.2. Ligand screening

The phytocompounds were extracted from extensive literature study. We examined anti-inflammatory properties these compounds in Duke's database. The most important phytochemical property Lipinski rule of five predicted using SWISSADME on-line server [18].

2.3. Molecular docking

Molecular docking analysis was performed using the geometry-based PatchDock algorithm [19]. pdb file format or PDB code of the receptor was used as the input file and all the molecules were given in pdb file format. Geometric Hashing algorithm applied for geometric fit and atomic desolvation energy accounted to evaluate docking transformation. RMSD (root mean square deviation) clustering is subjected to the docked complex solutions to discard the redundant solutions. The output file was as a docking report. The docked complexes were visualised by molecular graphics software tool “Pymol”

[20]. The interactions between the ligands and proteins were also perceived along with the length of the amino acids interaction and it was calculated by using Pymol. The binding energy was calculated according to Zhang et al. (1997) by atomic contact energy (ACE) [21].

3. Results and discussion

Due to unavailability of crystal structure of IL17 and IL17D proteins, abinitio modelling was performed to obtain the three dimensional structure. This was adept by I-TASSER server (Figure1a). As displayed in Figure2 Ramachandran plot of the IL17 and IL17D models were calculated which shows the 98.6 and 96.7 of all the amino acids resided in the maximum favored regions and also allowed regions respectively. These results revealed that IL17 and IL17D models were in good quality.

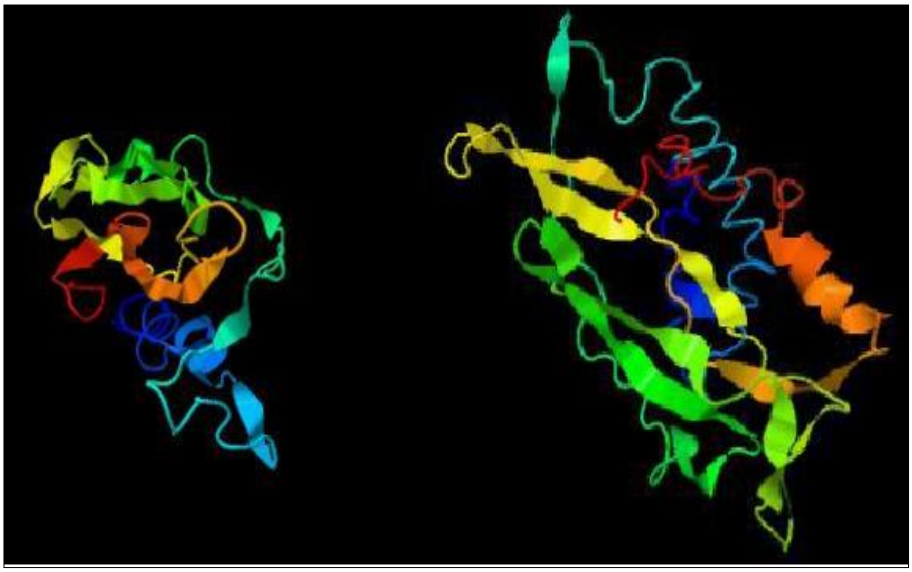

Figure 1. The modeled structure of IL17 and IL17D receptor proteins

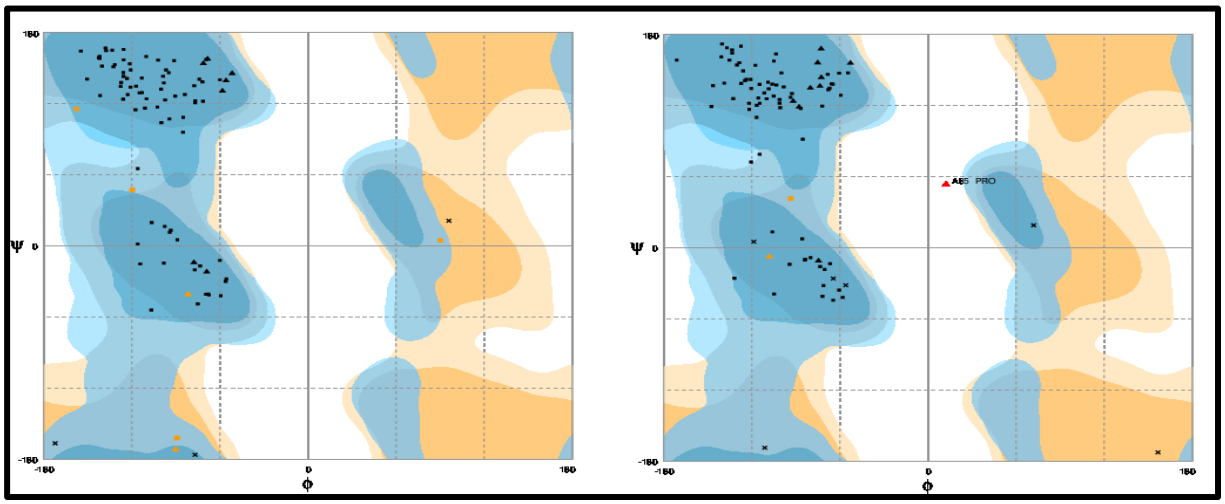

Figure 2. Structural validation of IL17 and IL17D proteins using Ramachandran plot

Totally five phytocompounds were identified with anti-inflammatory property by searching extensive literature survey. These compounds were subjected to the most important druglikeness property called Lipinski's rule of five [22]. The criteria of the Lipinski's rule of five are molecular weight (within 160–480), number of heavy atoms (within 20–70), lipophilicity (within 40–130), number of hydrogen bond donors (within 4–7), number of hydrogen bond acceptors (within 8–12). All the five compounds conformed to the above mentioned criterion and were further allowed to the molecular docking analysis using PatchDock software.

Table 1. Details of phytocompounds

S. No	Plant name	Phytocompound Name	Lipinski's rule of five
1.	*Tribulus terristis*	Citral	No violation
2.	*Cedrus deodora*	Centdarol	No violation
3.	*Desmodium gangeticum*	Genistein	No violation
4.	*Sida rhombitulia*	Ephedrine	No violation
5.	*Solanum indicum*	Rosmarinic acid	No violation

In the present study, molecular docking studies were carried out, to screen and identify potential phytocompound that can fit into the most favorable binding site, against IL17 and IL17D modeled protein. Missing hydrogens were added in the modeled structure proteins. Analysis of the complexed structure of Citral, Centdarol, Genistein, Ephedrine, Rosmaric acid with IL17 and IL17D were obtained by molecular docking analysis which further revealed the compounds bind almost at the same receptor site. The interaction and binding energy profiles of all the docked complexes were investigated, which showed that genistein binds more strongly at the receptor IL17 binding site and Citral binds more strongly at the receptor IL17D binding site respectively, than other compounds listed in Table 2.

Table 2. Docking result of IL17 and IL17D protein with phytocompound

S. No	Protein	Ligand	ACE	RMSD	Presence of H-Bond
1.	IL17	Citral	-188.95	4.0	No
2.	IL17	Centdarol	-167.86	4.0	No
3.	IL17	Genistein	-203.71	4.0	Yes
4.	IL17	Ephedrine	-117.96	4.0	Yes
5.	IL17	Rosmarinic acid	-140.01	4.0	Yes
6.	IL17D	Citral	-271.15	4.0	Yes

7.	IL17D	Centdarol	-189.17	4.0	Yes
8.	IL17D	Genistein	-226.70	4.0	No
9.	IL17D	Ephedrine	-170.85	4.0	No
10.	IL17D	Rosmarinic acid	-141.03	4.0	No

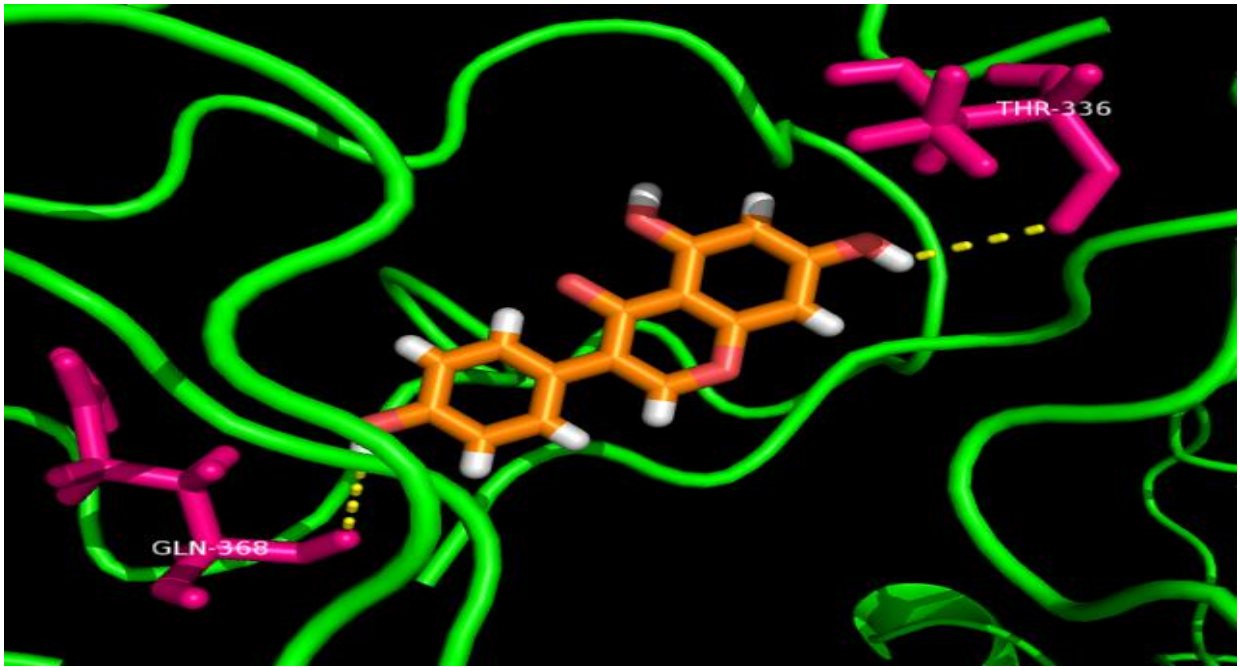

Figure 3. Cartoon representation of IL17 receptor – Genistein complex

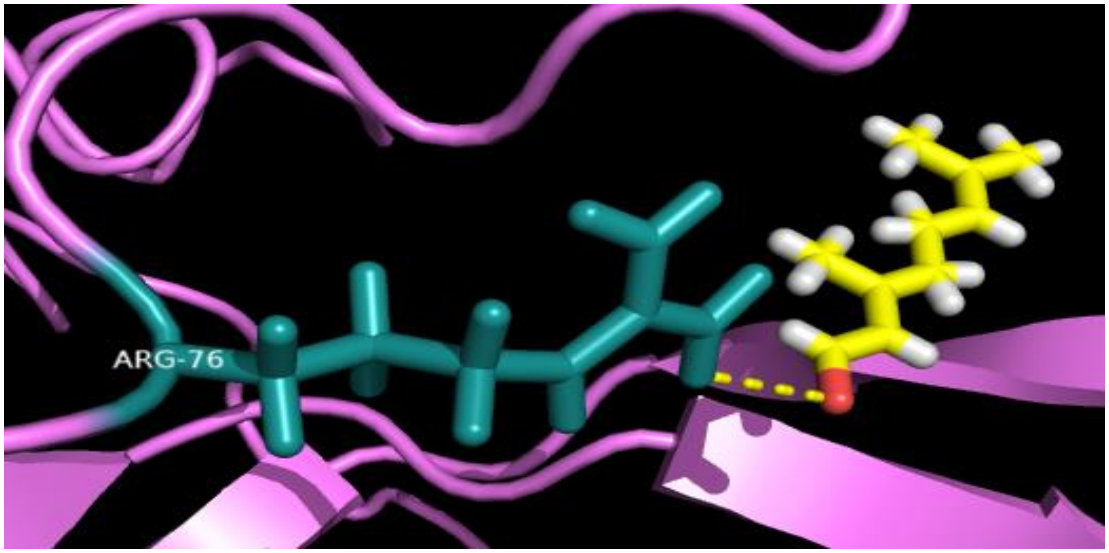

Figure 4. Cartoon representation of IL17D - Citral complex

Genistein forms two hydrogen bonds with IL17 receptor through THR336, GLN368 residues (Figure3). Similarly, IL17D interacts with citral compound through ARG76 residue (Figure4). IL-17 is the signature cytokine plays critical roles in tissue inflammation and pathogenesis of autoimmune diseases [23]. IL-17 levels have been identified to be elevated in the tissues and synovial fluid of RA patients [24], [25]. This study suggested that Genistein shows strong binding affinity with IL-17 which can affects the IL17 receptor functions. IL27 is other name of IL17D receptor, involve in both pro- and anti-inflammatory functions has been reported in arthritis. IL17D modulates osteoclast activity in joint diseases like rheumatoid arthritis [26]. Citral is the best inhibitor for IL17D receptor protein through ARG76 with low binding energy.

4. Conclusion

Plant-derived natural products provide an essential and promising resource of novel therapeutic agents for RA and other autoimmune diseases. Traditional systems of medicine practitioners mostly prefer to utilize herbal extracts, either individually or in a formulation using multiple herbs. Though, as part of its drug discovery process, the pharmaceutical industry often solicits purified herbal compounds which own bioactivity that replicates, although exceeds the bioactivity of the parental herbal extract. Thus, our in silico study shows that the compounds genistein and citral may have better efficacy and greater activity than the other phytocompounds and traditional inhibitors against IL-17 and IL-D cytokines. In future, howbeit these compounds have to be studied extensively using in vitro and in vivo approaches before possible use in clinical settings as an effective inhibitor.

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