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In silico molecular docking of selected polyphenols against interleukin-17A target in gouty arthritis

Haruna Isiyaku Umar*[1], Adeola Ajayi[1], Sunday Solomon Josiah[1], Tolulope Saliu[1], Jamilu Bala Danjuma[2], Prosper Obed Chukwuemeka[3]

[1] Department of Biochemistry, Federal University of Technology, P. M. B. 704, Akure, Ondo State, Nigeria

[2] Department of Biochemistry and Molecular Biology, Federal University, Birnin Kebbi, Kebbi State, Nigeria

[3] Department of Biotechnology, Federal University of Technology, Akure, Nigeria

*Correspondence author: Tel.: +2347033326006; E-mail: ariwajoye3@gmail.com

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ABSTRACT: The binding of interleukin-17A (IL-17A) to its receptor causes the release of chemokine which have an implication in the pathogenesis of gouty arthritis. Though, some synthetic drugs have been proved worthy as IL-17A inhibitors in the management of gout but they have been associated with a number of side effects. Polyphenols have been documented for numerous therapeutic applications. In spite of this, there are scarce data on the mechanism of action and protective potentials of polyphenolic against gouty arthritis. This present *in silico* study aimed to assess the inhibitory potentials and ADMET properties of selected polyphenols against IL-17A using molecular docking tools. The crystal structure of IL-17A was retrieved from the protein database, while the structures of polyphenolic compounds were retrieved from Pubchem. Drug-likeness of the polyphenols was assessed using DruLiTo. A total of 22 out of 26 polyphenols investigated passed the Lipinski drug likeness rule of five which were then docked with the active site of IL-17A using docking software, and the docked complexes were analyzed using LigPlot and protein-ligand profiler web server. The results showed that all the investigated polyphenols have appreciable higher binding affinity when compared to the standard drug (allopurinol) with pelargondin and catechin having the highest binding affinity (-7.5 kcal/mol). Furthermore, ADMET screening were carried out on the five compounds with the best hits. Conclusively, this *in silico* study suggests that these investigated polyphenols could serve as better replacements for synthetic drugs such as allopurinol in the management of gouty arthritis.

Keywords: Gouty arthritis; Inflammation; Interleukins; *In silico*; Phenolics; ADMET.

1. INTRODUCTION

Gout, a prevalent chronic arthritis with every 9.5% to 13.5% per 1,000 persons becoming affected [1, 2]. The pathophysiology of this disease is chiefly due to the improper uric acid metabolism leading to the precipitation and accumulation of uric acid crystals in joints, bones, tissues, and other organs [1]. Therefore, gout is also called hyperuricemia [3]. Gout is more common in male compared to female base on the ratio of 4:1. Although, the rate increases in women post-menopause [1, 4]. Furthermore, individuals with gout are at risk of developing chronic kidney disease, cardiovascular diseases, metabolic disorders, and psychosis [5-9].

During purine metabolism, hypoxanthine and xanthine are produced, and then metabolized in the liver to uric acid. The reaction is catalyzed by xanthine oxidase [10]. Humans lack uricase, an enzyme that degrades uric acid to soluble allantoin; therefore, uric acid is not degraded leading to the accumulation of insoluble uric acid crystals in joints, bones, and many other organs like kidney [11-13]. According to Kostalova et al. [10], xanthine oxidase is a key player in the pathogenesis of gouty arthritis and its inhibition is crucial in the management of the pathological condition [10].

Cytokines of the interleukin-17 family promote the maintenance of both adaptive and innate immunity [14-17]. Dysregulation of their production may contribute to inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis and asthma [14, 15, 17, 18]; as such, the aforementioned facts has drawn researchers' attention to target them for therapeutic purposes. The roles played by interleukins in protective immunity could be complicated by the aggravation of autoimmune diseases such as rheumatoid arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, autoimmune hepatitis and different forms of cancer development [19-21] as several studies have reported that serum or urinary levels of interleukin 17A (IL-17A) are significantly elevated in patients with these pathologies [22-27].

Interleukins play critical roles in the pathogenesis of gout especially IL-17A and IL-18 which are proinflammatory cytokines that are upregulated in the serum of gout patients [11, 22, 25]. Most notably, IL-17A is involved in the inflammatory process during infection and in the pathogenesis of chronic inflammation in autoimmune diseases via mediating the recruitment of neutrophils and macrophages during inflammation [19, 21, 28,]. IL-17A is a significant proinflammatory cytokine produced by T-helper 17 (Th17), gamma delta T (γδ T) and natural killer (NK) cells [29]. Previous reports have shown that IL-17 is present at sites of inflammatory arthritis and its synergistic interactions amplifies the inflammation induced by other cytokines, including IL-1, IL-6, IL-8, and TNF-α [19, 25, 28, 30]. In addition, Zhou et al. [31] reported that excess chemokines are released into the blood of gouty patients when IL-17A binds to its receptor.

Plants possess a wide variety of chemical compounds which are products of secondary metabolism and these phytoconstituents exhibit therapeutic properties including anti-inflammatory activity; which appear to have great potentials for synthesizing new drugs in the management of infectious diseases [32, 33]. Polyphenols, a wide family of phytochemicals with numerous biological properties, and this make them attract considerable attention. For instance, the immunomodulatory property polyphenols play a central role in the regulation of immune systems in humans [34]. Besides, the biological activities of polyphenols depend crucially on their chemical structures and the biotransformation undergone in the biological system [34]. Oliviero et al. [35] reported that polyphenols play a dual role in the management of gout arthritis viz; inhibition of xanthine oxidase thereby decreasing the production of uric acid and acting as an anti-inflammatory agent via inhibition of pro-inflammatory genes involved in canonical inflammatory and apoptotic pathways. The inhibited pathways are NF-κB signaling pathway which leads to IL-1 transcription and inflammasome activation which allows the release of IL-1 into the extracellular space [35].

Allopurinol is a drug used for long-term management of hyperuricemia. Mechanistically, allopurinol competitively inhibits xanthine oxidase, an enzyme responsible for uric acid production [36]. Though, synthetic drugs such as allopurinol are effective in the management of gouty arthritis which may be due to their ability to target and inhibit IL-17A, however, they are usually accompanied with several complications such as gastrointestinal distress, hypersensitivity reactions, skin rash, elevated blood glucose and pressure, diarrhea, and vomiting in patients [1, 37-39]. Therefore, it is pertinent to identify plant-based compounds with IL-17A inhibitory potential *in silico*. Hence, this present *in silico* study aimed to assess the inhibitory

potentials of selected polyphenols against IL-17A using molecular docking tools and screening the best hit compounds for their ADMET properties *in silico*.

2. MATERIALS AND METHODS

2.1. Macromolecule's structure retrieval and Prediction of active site

The structure of IL-17A (PDB ID: 4HR9) was retrieved from Protein Data Bank (PDB). Because IL-17A is a homodimer (chain A and B) protein, we only used chain A for our docking studies. The other chain and water molecules were removed using software tool Chimera©, version 1.13., (http://www.cgl.ucsf.edu/chimera), the proteins were prepared for docking by removing the co-crystallized ligand and additional water molecules to make it as a nascent receptor [40]. The binding pocket of the receptor was predicted via DogSite platform of protein-plus webserver (http://proteinsplus.zbh.uni-hamburg.de) base on the drugability of pockets identified [41]. The amino acid residues in the predicted pocket was further compared with those identified through extensive literature mining.

2.2. Ligands' structures retrieval and preparations

Twenty-six phenolic compounds vis; apigenin, caffeic acid, catechins, chlorogenic acid, *p*-coumaric acid, curcumin, cyanidin, ellagic acid, epicatechin, ferulic acid, gallic acid, genistein, glycitein, hesperetin, isoquercitrin, kaempferol, luteolin, malvidin, naringenin, pelargondin, pyrocatechol, pyrogallol, quercitrin, quercetin, resorcinol and rutin were selected for the ligand protein docking study. The docking study was performed against a standard drug (allopurinol). The molecular structures of the ligand (polyphenols) as well as that of the standard drug were retrieved from Pubchem database. The structures were retrieved in SDF format and were converted to mole files using MarvinSketch© (ver. 15.11.30). The molecules were then minimized using the Merck molecular force field (MMFF94) algorithm in Avogadro (ver. 1.10).

2.3. Drug likeliness screening

The selected molecules were screened for drug likeliness as described by Lipinski et al. [42]. The molecules were analyzed using DruLiTo software to calculate their logP, molecular weight, hydrogen bond donors and acceptors values. The lipinski's rule of five was applied to screen for the probable molecules [43].

2.4. Molecular docking

Auto Dock Vina [44] was utilized for the molecular docking analysis of the selected ligands with the protein target. The protein data bank, partial charge, and atom type (PDBQT) file of the protein was generated through this software (using the previously created PDB file as input). The specific target site of the protein was set -with the help of grid box. The X, Y, and Z dimensions were set to 38.39 × 25.00 × 32.25, the X, Y and Z centers were adjusted based on the active site reviewed from literatures of the protein target [1, 14, 25]. Once the molecular dockings were completed and 10 configurations for each protein-ligand complex were generated for all the compounds using the software, text files of scoring results were also generated for the purpose of manual comparative analysis. For each of the compounds, the docking runs were done ten (10) times consecutively with the number of modes set to 10 in order to enhance the accuracy and reliability of the outputs. The protein-ligand complexes were prepared with the aid of PyMOL© Molecular Graphics (version 1.3, 2010, Shrodinger LLC), as well as the 2D molecular interactions were visualized using BIOVIA Discovery Studio 2016 [45].

2.5. ADMET properties prediction of the best hit compounds

ADMET (Adsorption, Distribution, Metabolism, Excretion and Toxicity) is key to analyze the pharmacodynamics and pharmacokinetics of the compounds having best docking hits as they could be used as a drug. A two-step prediction was deployed to screen them for i) the aqueous solubility, druglikeness and medicinal chemistry filters with the aid of SWISSADME servers [46]; and ii) their ADMET properties with the aid of ADMETSar and SWISSADME servers [46-48].

3. RESULTS AND DISCUSSION

Over the years, plants are confirmed to have medicinal properties that were used in the management of many pathological conditions [49-54]. Though, traditional therapy has been overshadowed by modern medicine to manage human health. But, the past few decades have witnessed an increase in the application of phytomedicines for orthodox therapy [55]. Interleukin 17A have been implicated in the pathogenesis of gout arthritis [11, 22, 25] and available synthetic drugs are accompanied with a number of side effects alongside their therapeutic efficacies [1, 39]. Hence, in this present *in silico* study, we used molecular docking technique to investigate the ability of some polyphenolic compounds to inhibit the action of IL-17A.

Twenty-six (26) phenolic compounds and a reference drug (allopurinol) were selected and assessed for their inhibitory potentials against IL-17A. The structure of these compounds (ligands) was obtained from pubchem. For *in silico* analysis of phenolic compounds, the drug potential of all the ligands was accessed using the Lipinski's rule of five via the DruLiTo© software. Lipinski rule of five is a rule to evaluate drug likeness and to determine if a chemical compound possesses a certain pharmacological or biological activity to make it an orally active drug in humans [42, 43]. The compound that exceeds molecular weight (M_w) > 500 Da, calculated log P > 5, hydrogen-bond donors > 5 and hydrogen-bond acceptors >10 is unlikely to be further pursued as a potential drug, because it would likely lack properties essential for absorption, distribution, metabolism and excretion [42, 43, 56, 57]. The data we obtained from the drug likeliness screening revealed that 22 out of the 26 screened compounds passed the Lipinski's rule of five. Non-violation of drug likeliness rule by the 22 compounds indicates that these compounds will likely possess good absorption, molecular flexibility, oral bioavailability and ability to reach their target site of action when ingested [42, 43, 56, 57]. The four compounds that we eliminated from further docking analysis for violating at least one of the rules are chlorogenic acid, isoquercitrin, quercitrin and rutin (Table 1).

The 3D structure of IL-17A (4hr9) was retrieved from Protein Database (Fig. 1) with resolution of 2.48Å. IL-17A consist of 155 amino acid sequences; a disulfide-linked, homodimeric (chain A and B) secreted glycoprotein with a molecular mass of 35kDa [14, 21, 58]. The amino acid residues in the active site of IL-17A after extensive literature search are; Tyr43, Tyr44, Trp51, Leu53, Tyr62, Pro63, Val65, Ile66, Trp67, Ala69, Ile92, Gln94, Glu95, Ile96, Leu97, Val98, Leu99, Leu112, Lys114, Val117, Ser118, Val119, Glu120 and Cys121 [1, 14, 25]. A novelty was included in this study even though we were able to get the amino acid residues from literatures, DogSite platform from the protein-plus web server (http://proteinsplus.zbh.uni-hamburg.de) was deployed to predict the druggable pocket of the target receptor, IL-17A. according to [41], the pocket with the highest drug score is likely to be the binding site of a given receptor. As results of these, the predicted druggable pocket consist of the following amino acid residues; Pro19, Arg20, Thr21, Val22, Met23, Val24, Asn25, Leu26, Leu99, Glu102, Asn108, Ser109, Phe110, Arg111 and Leu112.

Table 1. Lipinski properties of selected polyphenols analyzed using DruLiTo© software tool.

S. No	Name of compound	PubChem ID	Molecular weight (<500Da)	logP (<5)	No of HB donor (5)	No of HB acceptor (10)	No of violations
1.	Allopurinol	135401907	136.04	-0.443	2	5	0
2.	Apigenin	5280443	270.05	1.138	3	5	0
3.	Caffeic acid	689043	180.04	0.888	3	4	0
4.	Catechin	73160	290.08	0.852	5	6	0
5.	Chlorogenic acid	1794427	354.1	-0.7	6	9	1
6.	p-Coumaric acid	1549106	164.05	0.751	2	3	0
7.	Curcumin	9695161	368.13	1.945	2	6	0
8.	Cyanidin	128861	287.06	1.967	5	5	0
9.	Ellagic acid	5281855	302.01	1.366	4	8	0
10.	Epicatechin	72276	290.08	0.852	5	6	0
11.	Ferulic acid	445858	194.06	0.78	2	4	0
12.	Gallic acid	370	170.02	0.964	4	5	0
13.	Genistein	5280961	270.05	1.043	3	5	0
14.	Glycitein	5317750	284.07	1.364	2	5	0
15.	Hesperetin	72281	302.08	1.03	3	6	0
16.	Isoquercitrin	5280804	464.1	0.099	8	12	2
17.	Kaempferol	5280863	286.05	1.486	4	6	0
18.	Luteolin	5280445	286.05	1.486	4	6	0
19.	Malvidin	159287	331.08	2.099	4	6	0
20.	Naringenin	932	272.07	0.79	3	5	0
21.	Pelargondin	440832	271.06	1.619	4	4	0
22.	Pyrocatechol	289	110.04	1.083	2	2	0
23.	Pyrogallol	1057	126.03	1.431	3	3	0
24.	Quercitrin	5280459	448.1	0.802	7	11	2
25.	Quecertin	5280343	302.04	1.834	5	7	0
26.	Resorcinol	5054	110.04	0.654	2	2	0
27.	Rutin	5280805	610.15	-0.735	10	16	3

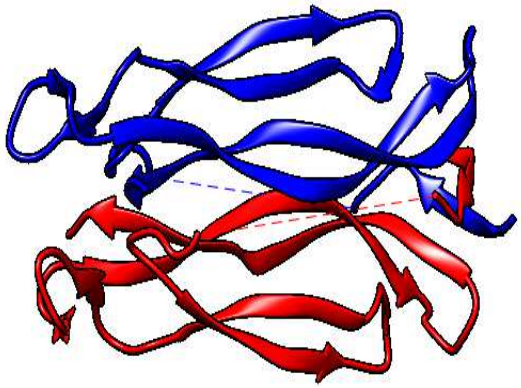

Figure 1. Three dimensional and homodimeric structure of interleukin-17A. Chain A in blue and chain B in red.

Autodock Vina in Python Prescription 0.8 suite, PyMOL, and Discovery studio 2016 were used to determine the binding energies, binding poses, and best orientation of ligands with targets as shown in Table 2 and Fig. 2. Results from this research study indicated that the binding affinity between the ligands and IL-17A

were stabilized by non-covalent bonds such as hydrogen bonds, hydrophobic bonds and pie-type interactions. One of the long-standing intentions of structural biologists is to broadly define the specific roles of hydrogen bonds in protein structures and functions [59]. The effect of hydrogen bonding in stabilizing the molecular interaction between the ligands and the protein cannot be ignored because of its critical roles in enzyme catalysis, protein-substrate and protein-inhibitor complexes, as well as structural stability of various biological molecules [60]. In addition, the capacity to possess a positive charge at the physiological pH despite being in covalent bond within molecules is a unique feature possessed by it [60]. Similarly, hydrophobic interactions are considered to be indispensable in many systems such as micelles, vesicles, colloids, membranes and transport; self-organization, polymer interactions, protein folding and ligand binding, nucleic acids, drug action, and water-mediated organic reaction. Indeed, hydrophobic interaction is one of the most reverent intermolecular forces [59]. Recently, researchers have reported that the binding affinity of ligands to a target protein is directly proportional with the hydrophobic interactions between the ligands and the hydrophobic amino acid residues found in the target's binding site [60, 61]. This could have actually accounted for the appreciable binding affinity of 19 out of the 22 compounds docked against IL-17A studied in this work as compared to allopurinol (Fig. 2).

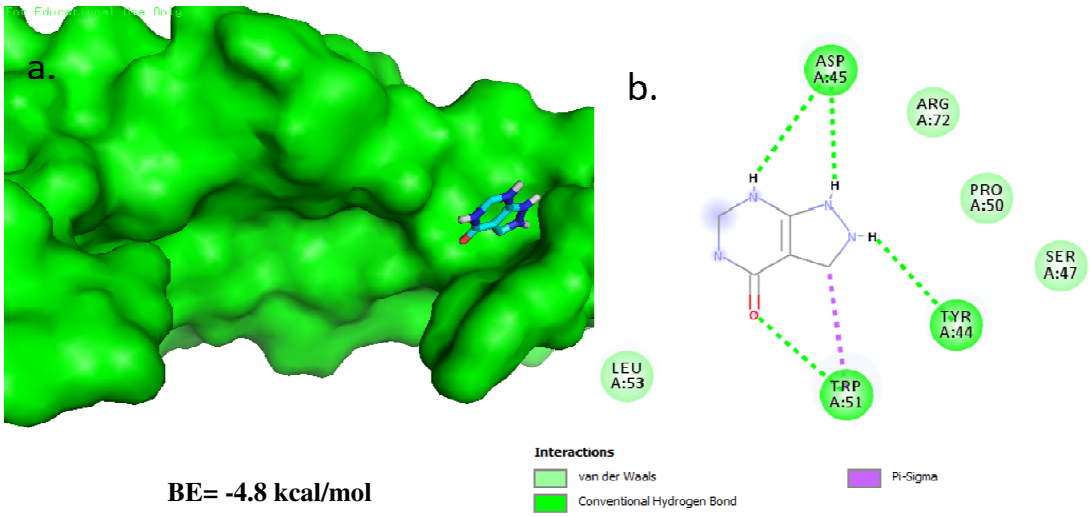

Figure 2. Molecular docking of Allopurinol with IL-17A. a) 3D binding pose of allopurinol after docking experiment with IL-17A generated using PyMOL. Allopurinol binds to a different site on IL-17A. b) 2D interaction prepared using Discovery Studio.

The results of this study revealed that interaction between allopurinol and the selected polyphenols with the amino acid residues within the active site of IL-17A (Fig. 2-3). In other words, all investigated compounds fit into the active cavity of IL-17A, an achievement that might likely prevent IL-17A to bind with its receptor, consequently preventing the release of chemokines. Allopurinol, one the most commonly used xanthine oxidase inhibitor, reduces oxidative stress in the vasculature, improves endothelial function in a variety of cardiovascular disease states, and reduces expression of proinflammatory molecules such as soluble intercellular adhesion molecule-1 (ICAM-1) *in vitro* [62]. The findings from this present *in silico* study showed that when compared with the selected polyphenols, allopurinol had the highest (least effective) binding energy of -4.8 kcal/mol when docked with IL-17A which resulted in the formation of hydrogen bond with Tyr44, Asp45 and Trp51; hydrophobic interaction with Ser47, Pro50, Trp51, Leu53 and Arg72 and an

additional interaction with Trp51 via π-stacking (Fig. 2 and Table 2). Both catechin and pelargondin had the lowest (most effective) binding energy of -7.5 kcal/mol (Table 2). Catechin formed hydrogen bond with Asn108 and Phe110; also, established hydrophobic interaction with Val24, Leu26, Leu99, Phe110, Arg111 and Leu112 while pelargondin established hydrophobic interaction with Arg20, Thr21, Val22, Leu26, Leu99, Ser109, Phe110 and Arg111 when docked against IL-17A; it aromatic rings interacted with Val22, Val24 and Leu112 through pie bond formation. Pelargondin formed no hydrogen bond but majorly hydrophobic and pie-bonds with Arg20, Thr21, Met23, Leu26, Leu99, Asn108 and Leu112; and Val22, Val24 and Phe110 respectively. The interactions exhibited by these polyphenols agree with previous findings that these amino acid residues are involved in their contact with IL-17A receptor [14, 21]. From our findings, 19 polyphenols exhibited better interactions with amino acid residues in the active site of IL-17A than allopurinol which might be responsible for their better binding affinities.

Table 2. Binding energy and molecular interactions of selected polyphenols with interleukin-17A.

Name of compound	Binding energy (kcal/mol)	No of H-bond formed	H-Bond interaction residues	Distance (Å)	Hydrophobic interactions	Residues forming π-interactions
Allopurinol	-4.8	3	Tyr44, Asp45 and Trp51	2.97	Ser47, Pro50, Trp51, Leu53 and Arg72	Trp51
Apigenin	-7.0	1	Arg20	2.86	Arg20, Val24, Leu26, Leu99, Asn108, Phe110 and Leu112	-
Caffeic acid	-5.8	2	Asn108 and Phe110	2.84 and 2.87	Val24, Leu26, Leu99, Phe110, Arg111 and Leu112	-
Catechin	-7.5	2	Asn108 and Phe110	3.29 and 3.28	Arg20, Thr21, Val22, Leu26, Leu99, Ser109, Phe110 and Arg111	Val22, Val24 and Leu112
Curcumin	-6.7	1	Leu112	3.26	Val22, Met23, Val24, Leu26, Leu99, Phe110 and Arg111	-
Cyanidin	-6.5	3	Tyr44, Trp51 and Val119	2.91, 3.28 and 3.21	Tyr43, Tyr44, Asp45 and Trp51	-
Ellagic acid	-6.4	2	Arg20 and Phe110	2.92 and 3.01	Val22, Val24, Leu99, Arg111 and Leu112	-
Epicatechin	-7.3	3	Asn108 and Phe110	5.28 and 3.06 (2.85)	Val22, Met23, Val24, Pro107, Ser109, Arg111 and Leu112	Val24, Leu26, Leu99 and Phe110
Ferulic acid	-5.5	4	Tyr43, Tyr44, Asp45 and Trp51	3.19, 3.10, 2.97 and 3.20	Tyr44 and Leu53	Tyr44
Gallic acid	-5.1	2	Val24 and Phe110*	3.24 and 2.92 (3.07), (2.87)	Val24, Leu99 and Asn108	Phe110
Genistein	-6.6	3	Thr48, Thr122 and Cys123	3.88, 3.08 and 4.00	Tyr44, Ser47, Thr48, Trp51, Ile92, Gly120 and Cys121	Tyr44
Glycitein	-6.6	2	Thr48 and Thr122	3.04 and 2.82	Tyr44, Ser47, Thr48, Trp51, Ile92, Gly120, Cys121 and Thr122	Tyr44
Hesperetin	-6.6	2	Thr122 and Cys123	3.12 and 2.99	Tyr44, Ser47, Ser49, Trp51, Ile92,Val119, Gly120, Cys121 and Thr122	Tyr44
Kaempferol	-7.3	2	Val24 and Phe110	3.07 and 3.72	Arg20, Thr21, Met23, Leu26, Leu99, Ser109 and Arg111	Val22, Val24, Phe110 and Leu112

Name of compound	Binding energy (kcal/mol)	No of H-bond formed	H-Bond interaction residues	Distance (Å)	Hydrophobic interactions	Residues forming π-interactions
Luteolin	-6.9	1	Leu112	3.92	Val22, Val24, Leu26, Leu99, Phe110, Arg111 and Leu112	-
Malvidin	-6.3	3	Tyr43, Asp45, Trp51	3.61, 3.61 and 3.28	Tyr43, Tyr44, Asp45, Trp51, Leu53, Trp67and Val119	Tyr44
Naringenin	-7.1	-	-	-	Val22, Val24, Leu26, Leu99, Asn108, Phe110 and Leu112	-
p-Coumaric acid	-5.1	2	Val22 and Val24	2.94 and 2.99	Val22, Met23, Leu99, Phe110 and Leu112	-
Pelargondin	-7.5	-	-	-	Arg20, Thr21, Met23, Leu26, Leu99, Asn108 and Leu112	Val22, Val24 and Phe110
Pyrocatechol	-4.1	1	Phe110	3.15	Val24, Leu99, Asn108 and Ser109	Phe110
Pyrogallol	-4.8	4	Tyr43, Tyr44, Asp45 and Trp51	3.09, 2.90, 3.00 and 2.74	Tyr43	Tyr44
Quercetin	-7.4	3	Val24 and Phe110	3.28 (4.17) and 3.05	Arg20, Thr21, Met23, Leu26, Leu99, Ser109 and Arg111	Val22, Val24 and Phe110
Resorcinol	-4.4	4	Tyr43, Tyr44, Asp45 and Trp51	3.02, 2.98, 3.18 and 2.72	Tyr43, Tyr44 and Asp45	Tyr44

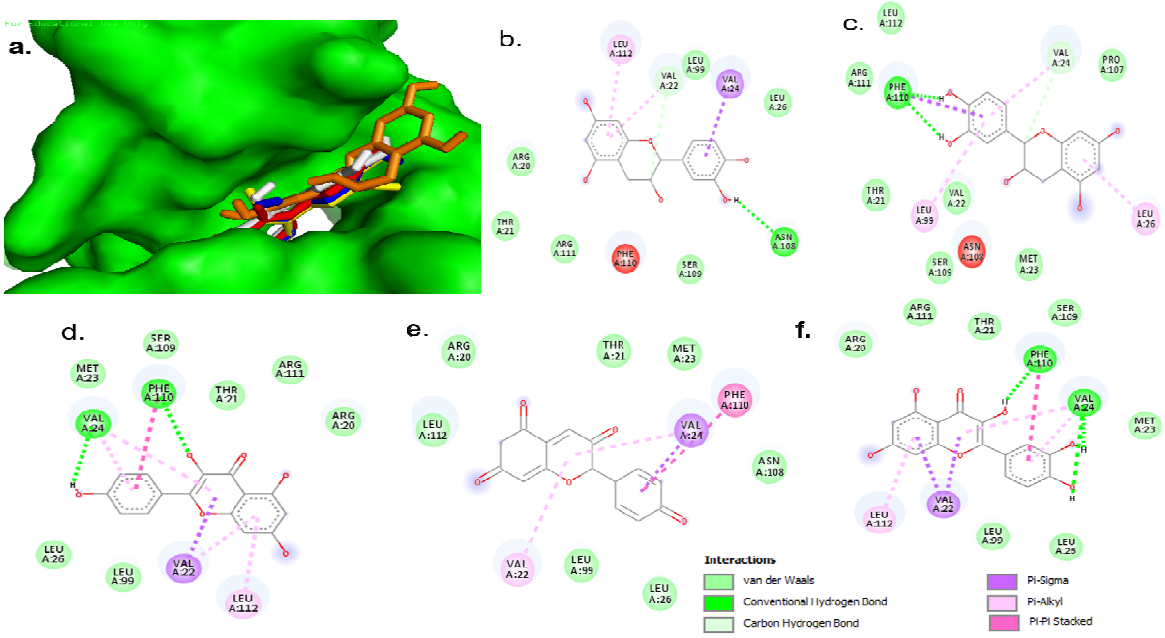

Figure 3. Molecular docking of five hit compounds with IL-17A. a) 3D binding pose catechin (white), epicatechin (orange), kaempferol (blue), pelargondin (red) and quercetin (yellow) bind to the same site on IL-17A. 2D interactions of b) catechin, c) epicatechin, d) kaempferol, e) pelargondin and f) quercetin with the amino acid residues of IL-17A.

Polyphenols belongs to the class of naturally occurring compounds that are mostly found in vegetables, fruits, beverages, and cereals [34]. More than 500 unique polyphenols are collectively called phytochemicals. It has been documented that regular consumption of polyphenol-rich diets is beneficial for the brain and cardiovascular system, as well as the immune system [34]. Owing to their extensive pharmacological and

bioactive properties, polyphenols are widely studied and demonstrated their usefulness in the prevention and treatment of disease [63]. The anti-inflammatory and immunomodulatory activity of polyphenols have attracted huge attention for years [35]. It is shown that continuous and long-lasting inflammation can be the major cause of cardiovascular diseases, cancer, neurodegenerative diseases, diabetes type II, arthritis, and obesity [64]. In this regard, the anti-inflammatory characteristic of polyphenols is contributed to their antioxidant activity, such as ROS scavenging in addition to their ability to alter the expression of several pro-inflammatory genes like nitric oxide synthases, cyclooxygenase, multiple cytokines, and lipoxygenases [34, 35, 63, 64]. Conversely, polyphenols modulate the immune system through the modification in cytokines production, immune cell populations, and pro-inflammatory gene expression [34]. According to Fan et al. [65], catechin exhibit anti-inflammatory properties via the regulation of NF-kB, MAPKs and Nrf2 pathways. Pelargondin has been reported to be the main anthocyanin in fruits and vegetables that is responsible for the anti-inflammatory effect, antioxidant and antidiabetic potentials *in vivo* [63, 64, 66]. According to Li et al. [67], quercetin, found in fruits, vegetables, leaves and grains; is known for anti-inflammatory potentials, mast cell stabilizing and gastro-intestinal cytoprotective activity. Epicatechin, an isomer of catechin, was reported to inhibit TNF-α, IL-6, PGE2 and Nitric oxide by Wang and Cao [68]. Kaempferol is majorly from *Zingiberaceae kaempferia* which its numerous beneficial functions had been reported as cardiovascular, antioxidant, antidiabetic, anti-inflammatory, hepatoprotective and neuroprotctive effects [69]. Naringenin is mainly found in citrus fruits such as lemon, orange, tangerine and grapefruit, it inhibits inflammation stimuli in several models of inflammatory pain [70, 71]. Apigenin is present principally as glycosylated in significant amount in onions, oranges, chamomile, thyme, tea, beer, and wine [72]. According to Fidelis et al. [73], a huge number of reports in the literature have confirmed the antioxidant properties of apigenin. In addition, anti-hyperglycemic [74], anti-inflammatory [75], and anti-apoptotic effects (in myocardial ischemia) [76] have been reported. Numerous pharmacological activities, including antioxidant and antimicrobial properties, have been attributed to curcumin [77]. Hesperetin is mainly found in citrus fruits; an aglycone of hesperidin, possesses a well-documented antioxidant efficacy as reported to have prevented inflammation and apoptosis as evidenced by its ability to lowering the levels of proinflammatory cytokines and caspase-3 activity in diabetic rats [78, 79]. The high binding affinities observed among the selected polyphenols in this *in silico* study might be a major contributor to their extensive bioactive and pharmacological properties.

After the *in silico* molecular docking analysis, 17 compounds with binding energies below -6.0 Kcal/mol to the least (Table 2) were chosen and their aqueous solubility, druglikeness filters and medicinal chemistry predicted through SwissAdme server (Table 3). All the compounds are soluble in water as predicted which are in an agreement with their predicted lipophilicity (Table 1). The druglikeness filters predicted herein are lipinski's, Ghose's, Veber's, Egan's and Muegge's. 12 compounds show no violations to these filters. The bioavailability scores range were good except for chlorogenic acid. 6 compounds were predicted to have one problematic fragment (in these case catechol A) under PAINS (for pan assay interference compounds, that is frequent hitters or promiscuous compounds) [46]. 15 compounds show leadlikeness ability. Finally, the ease to modify these compounds fall between 1.76 and 4.16.

Furthermore, 5 hit compounds (Table 2) namely; catechin, epicatechin, kaempferol, pelargondin and quercetin with allopurinol, were screened for their ADMET properties using ADMETSar and SwissAdme servers [46-48]. Table 4 show the classes and properties predicted for these compounds. Allopurinol was predicted to permeant the blood-brain barrier, quercetin had a low human oral availability and it might serve as substrate to p-glycoprotein (also pelargondin).

Table 3. Aqueous solubility, druglikeness and medicinal value of phenolic compounds with binding energy between -6.0 kcal/mol and -7.5 kcal/mol including our control drugs predicted using SWISSADME server.

Compound Name	Water Solubility (Log *S*)	Lipinski's filter (Pfizer)	Ghoose filter	Veber Filter (GSK)	Egan Filter (Pharmacia)	Muegge Filter (Bayer)	Bioavailability score	PAINS	Leadlikeness	Synthetic accessibility
Allupurinol	Very soluble	Yes	No, violates MW<160, MR<40, #atoms<20	Yes	Yes	No, violates MW<200	0.55	0 alerts	No, violates MW<250	1.76
Apigenin	Moderately soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	Yes	2.96
Catechins	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	1 alerts; catechol	Yes	3.50
Chlorogenic acid	Very soluble	Yes, but violates H-don>5	No, violates WlogP<-0.4	No, TPSA>140	No, TPSA>131.6	No, violates TPSA>150, H-don>5	0.11	1 alerts; catechol A	No, violates MW>350	4.16
Curcumin	Moderately soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	No, violates MW>350, Rotors>7	2.97
Cyanidin	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	1 alerts; catechol A	Yes	3.15
Ellagic acid	Soluble	Yes	Yes	No, TPSA>140	No, TPSA>131.6	Yes	0.55	1 alerts; catechol A	Yes	3.17
Epicatechin	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	1 alerts; catechol A	Yes	3.50
Genistein	Moderately soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	Yes	2.87
Glycitein	Moderately soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	Yes	2.95
Hesperetin	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	Yes	3.22
Kaempferol	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	Yes	3.14
Luteolin	Moderately soluble	Yes	Yes	Yes	Yes	Yes	0.55	1 alerts; catechol A	Yes	3.02
Malvidin	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	Yes	3.33
Naringenin	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	Yes	3.01
Pelargondin	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	0	Yes	3.04
Quercetin	Soluble	Yes	Yes	Yes	Yes	Yes	0.55	1 alerts; catechol A	Yes	3.23

PAINS = pan assay interference compounds; MW = Molecular weight; MR = Molar refractivity; TPSA = topological surface area; WlogP = lipophilicity; H-don = Hydrogen bond donors; #atoms = No of atoms.

Table 4. ADMET properties of some selected drugs approved globally for the management of Covid-19 patients.

Class	Properties	Allopurinol	Catechin	Epicatechin	Kaempferol	Pelargondin	Quercetin
Absorption	BBB (Blood–Brain Barrier) permeability	Yes	No	No	No	No	No
	Caco-2 permeability	No	No	No	No	No	No
	Gastrointestinal Absorption	High	High	High	High	High	High
	Human Oral Availability	Moderate	Moderate	Moderate	Moderate	Moderate	Low
	Pgp-inhibitor	No	No	No	No	No	No
	Pgp-substrate	No	No	Yes	No	Yes	Yes
Distribution	PPB (Plasma Protein Binding)	21.7% (low)	112.0% (high)	112.0% (high)	106.1% (high)	102.8% (high)	117.5% (high)
	Sub-cellular localization	Mitochondria	Mitochondria	Mitochondria	Mitochondria	Nucleus	Mitochondria
Metabolism	CYP450 1A2 inhibition	No	No	No	Yes	Yes	Yes
	CYP450 3A4 inhibition	No	No	No	Yes	No	Yes
	CYP450 3A4 substrate	No	No	No	Yes	No	No
	CYP450 2C9 inhibition	No	No	No	Yes	Yes	No
	CYP450 2C9 substrate	No	No	No	No	No	No
	CYP450 2C19 inhibition	No	No	No	Yes	Yes	No
	CYP450 2D6 inhibition	No	No	No	No	Yes	Yes
	CYP450 2D6 substrate	No	Yes	Yes	No	No	No
	CYP inhibitory promiscuity	Low	Low	Low	High	High	High
	UGT catalyzed	No	Yes	Yes	Yes	Yes	Yes
Excretion	Skin permeation	-7.61 cm/s	-7.82 cm/s	-7.82 cm/s	-6.70 cm/s	-7.15 cm/s	-7.05 cm/s
Toxicity	Acute Oral Toxicity	Class iii	Class iv	Class iv	Class ii	Class ii	Class ii
	hERG Inhibitor	No	No	No	No	No	No
	Human Hepatotoxicity	Yes	No	No	Yes	Yes	No
	Ames Mutagenicity	Yes	Yes	Yes	Yes	No	No
	Carcinogens	No	No	No	No	No	No

All the compounds were predicted to be localized in the mitochondria except pelargondin (nucleus). Allopurinol show low plasma protein binding while the remaining compounds show otherwise. The poor binding of a compound to the plasma protein alters its efficacy to travel through plasma membrane. The prediction of their metabolism indicates that 3 compounds might inhibit CYP450 1A2 and 3A4 except pelargondin (with CYP450 3A4). Also, kaempferol and pelargondin were predicted to be inhibitors of CYP 2C9 and 2C19. Pelargondin and quercetin were predicted to inhibit CYP 2D6; while catechin and its isomer, epicatechin might be metabolized by CYP 2D6. The toxicity profile indicates that none of these compounds

were potential carcinogens, and no ability to inhibit hERG. Although, 3 of the compounds were predicted to be hepatotoxic while 4 compounds show AMES mutagenicity.

4. CONCLUSION

In conclusion, the phenolic compounds displayed promising association to the binding site of IL-17A *in silico* and displayed some level of safety through the ADMET screening than allopurinol. Hence, this study proposes that these polyphenols could serve as better replacements for synthetic drugs such as allopurinol in the management of gouty arthritis. Prominently, the outcome from this study suggests a need to develop drugs for the management of gouty arthritis from plant-derived compounds. However, this *in silico* study is just a means of predicting the activity of the bioactive compounds presents in plants; so, we strongly recommend further studies to validate the efficacy of these phenolic compounds in the management of gouty arthritis.

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