Original Article

Investigating Computational Insights Into Plant-derived Terpenoids of Bangladesh: Prospects for Anti-rheumatoid Arthritis Medication

Md Monirul Islam[1*], Iqbal Mahmud[2], Md Habibur Rahaman[3], S.M. Asaduzzaman[3]

1. Department of Pharmacy, Noakhali Science and Technology University, Noakhali, Bangladesh.
2. Department of Biochemistry and Molecular Biology, National University, Dhaka, Bangladesh.
3. Department of Pharmacy, East West University, Dhaka, Bangladesh.

*** Corresponding Author:**
S.M. Monirul Islam
Address: Department of Pharmacy, Noakhali Science and Technology University, Noakhali, Bangladesh.
Phone: +880 (16) 88287707
E-mail: monirul.phrm@nstu.edu.bd

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ABSTRACT

Background: Rheumatoid arthritis (RA) is characterized by autoimmunity, joint inflammation, and cartilage degradation. Numerous substances from plant sources, including terpenoids could treat RA.

Objectives: This study explores the potential of terpenoids from Bangladeshi plants as anti-RA medications by in silico studies.

Methods: Compounds were tested for favorable pharmacokinetic characteristics and binding affinities with the target proteins. Bauchampine A, betulinic acid, curcumol, geniposide, glycyrrhetinic acid, and paeoniflorin were selected for in-silico studies. Several protein targets were selected based on their role in the RA pathogenesis, including peptidyl-prolyl cis-trans isomerase FKBP1A, caspase 8 (CASP8), Bruton tyrosine kinase (BTK), interleukin 6, chemokine (C-C motif) ligand 20, tumor necrosis factor α, and stromal cell-derived factor 1. The compounds' pharmacokinetics and toxicity profiling were performed with the help of the online server. Both the compounds and receptors were prepared for further analysis using computational tools. Finally, molecular docking was performed with the help of AutoDock tools. The binding information was displayed in both numerical and pictorial ways.

Results: The selected compounds showed satisfactory values in terms of pharmacokinetic and toxicity parameters. The molecular docking analysis revealed a significant binding affinity with the target proteins. The highest binding affinity was found for bauchampine A with BTK (-7.2 Kcal/mol), betulinic acid with chemokine (C-C motif) ligand 20 (-8.8 Kcal/mol), curcumol with, tumor necrosis factor α (-8.8 Kcal/mol), geniposide with, tumor necrosis factor α (-8.7 Kcal/mol), glycyrrhetinic acid with BTK (-9.4 Kcal/mol), and papeoniflorin with BTK (-8.7 Kcal/mol).

Conclusion: Natural remedy for RA is preferred as it has minimal side effects. Accordingly, plant-derived terpenoids can be effective leads for developing RA medications.

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that is inflammatory and persistent, and linked to early mortality, systemic complications, and progressive disability [1]. Numerous illnesses, including lung conditions, kidney problems, and cardiovascular and cerebrovascular disorders, can coexist with RA. The development of RA is influenced by several risk factors, including environmental and genetic variables [2]. Medications for RA therapy are being developed. These medications include glucocorticoids, methotrexate, Janus kinase inhibitors, and interleukin (IL)-6 inhibitors, as well as nonsteroidal anti-inflammatory medicines (e.g. aspirin, ibuprofen, and naproxen) [3]. However, each class of these medications has its side effects [4, 5]. Plant-based natural remedies are usually considered safe and effective medications with reduced adverse effects [6, 7].

Numerous preclinical studies have shown that natural plant extracts and compounds reduce RA symptoms considerably [8-10]. Plant secondary metabolites are known as bioactive substances. Because of the enormous variation in their structures, they have a wide range of pharmacological activities and are useful in the treatment and prevention of many different diseases [11]. Several plants are used traditionally for the treatment of RA. These plants contain a variety of secondary metabolites. Terpenoids are the largest plant compound group, having numerous pharmacological activities, including antitumor, anti-inflammatory, antibacterial, antiviral, and antimalarial activities [12]. Nevertheless, in-depth research has not been done to determine whether these compounds can certainly be used to treat RA. For rational drug design, computational drug design forecasts molecular-level interactions between therapeutic drugs and targets. This meticulous methodology increases the likelihood of discovering medicinal compounds with minimal adverse effects. Molecular docking can be used to virtually screen large compound libraries, which can help guide optimization [13]. Therefore, we focus on the evaluation of anti-RA properties of terpenoids of some Bangladeshi plants by molecular docking analysis and perform the pharmacokinetic evaluation. This study can be helpful in synthesizing novel and safe medications for RA.

Materials and Methods

Ligand selection and preparation

An extensive literature survey was performed to find out the plant sources used for the treatment of RA. Then, the responsible plant compounds were also listed in the databases. Among the different classes of compounds, we selected only the terpenoids. Due to the anti-inflammatory activity of terpenoids, these compounds can be used to suppress RA-related symptoms [14-17]. The plants that are available in Bangladesh were finally selected. These compounds show their anti-RA activity by various mechanisms. For example, betulinic acid showed chondroprotective activity [18], curcumol had an immunoregulatory effect [19], geniposide revealed both anti-inflammatory [20] and immunosuppressive activities [21], paeoniflorin possessed antioxidant and anti-inflammatory activities [22]. The list of the selected compounds is provided in Table 1.

The six compounds were used as ligands for the subsequent in silico studies. After that, the 3D conformer of the ligands was obtained in structure data file format from the PubChem database [23, 24].

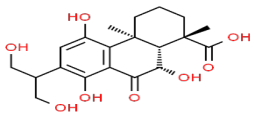
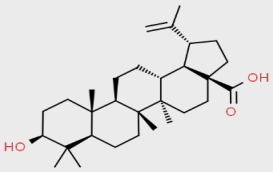
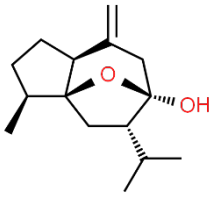
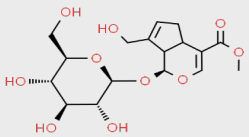
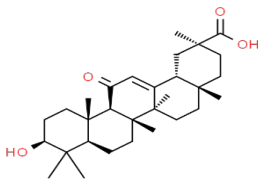
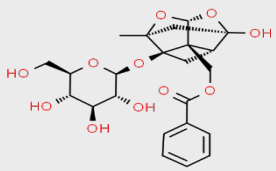
Absorption, distribution, metabolism, excretion and toxicity analysis

Pharmacokinetics studies the drug molecules' absorption, distribution, metabolism, and excretion (ADME) characteristics, which is essential in drug design procedures. Computationally, all these attributes form the basis of computer-based drug design. Inappropriate compounds are also eliminated based on these characteristics. The Swiss-ADME website is used to evaluate preliminary pharmacokinetics results during the drug discovery process. The Swiss-ADME online website is a public web server for predicting small compounds' pharmacokinetics and drug-likeness characteristics [25]. When developing new medications, toxicity evaluation may be done to evaluate a chemical's adverse or harmful effects [26]. In this regard, the pkCSM internet server was implemented for quickly analyzing toxicological properties, which is accessible to the public [27].

Receptor protein selection and preparation

RA is an autoimmune disorder that mainly affects the bone joint and causes severe pain and swelling at the affected places. There are several pathways involved in the progression of the disease. Since cytokines are intimately implicated in the RA process, they have long been

Table 1. List of plant derived terpenoid compounds having anti-RA properties [24]

SL	Compound Name	PubChem ID	Structure	Botanical Source	Bengali Name of Plant
1	Bauchampine A	135397554		*Bauhinia championii* (Benth.)	Kanchon
2	Betulinic acid	64971		*Ziziphus mauritiana* (Lam.), *Tetracera boliviana*	Kul, Boroi
3	Curcumol	14240392		*Curcuma zedoaria* (Christm.)	Shoti
4	Geniposide	107848		*Gardenia jasminoides* (J.Ellis)	Gandharaj
5	Glycyrrhetinic acid	44435791		*Glycyrrhiza glabra* (L.)	Josthi modhu
6	Paeoniflorin	442534		*Paeonia lactiflora* (Pall.)	Peony flower

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investigated and evaluated as possible targets of RA. Patients with RA may have high levels of inflammatory cytokines (including tumor necrosis factor-α [TNF-α], IL-6) in their peripheral blood or serum or synovium [28, 29]. According to research, chemokines influence angiogenesis and draw leukocytes, which contribute to the underlying pathophysiology of RA. The CXC and CC chemokines play vital roles in this process [30, 31]. Peptidyl-prolyl cis-trans isomerase FKBP1A, Bruton tyrosine kinase (BTK), and caspase 8 (CASP8) are also

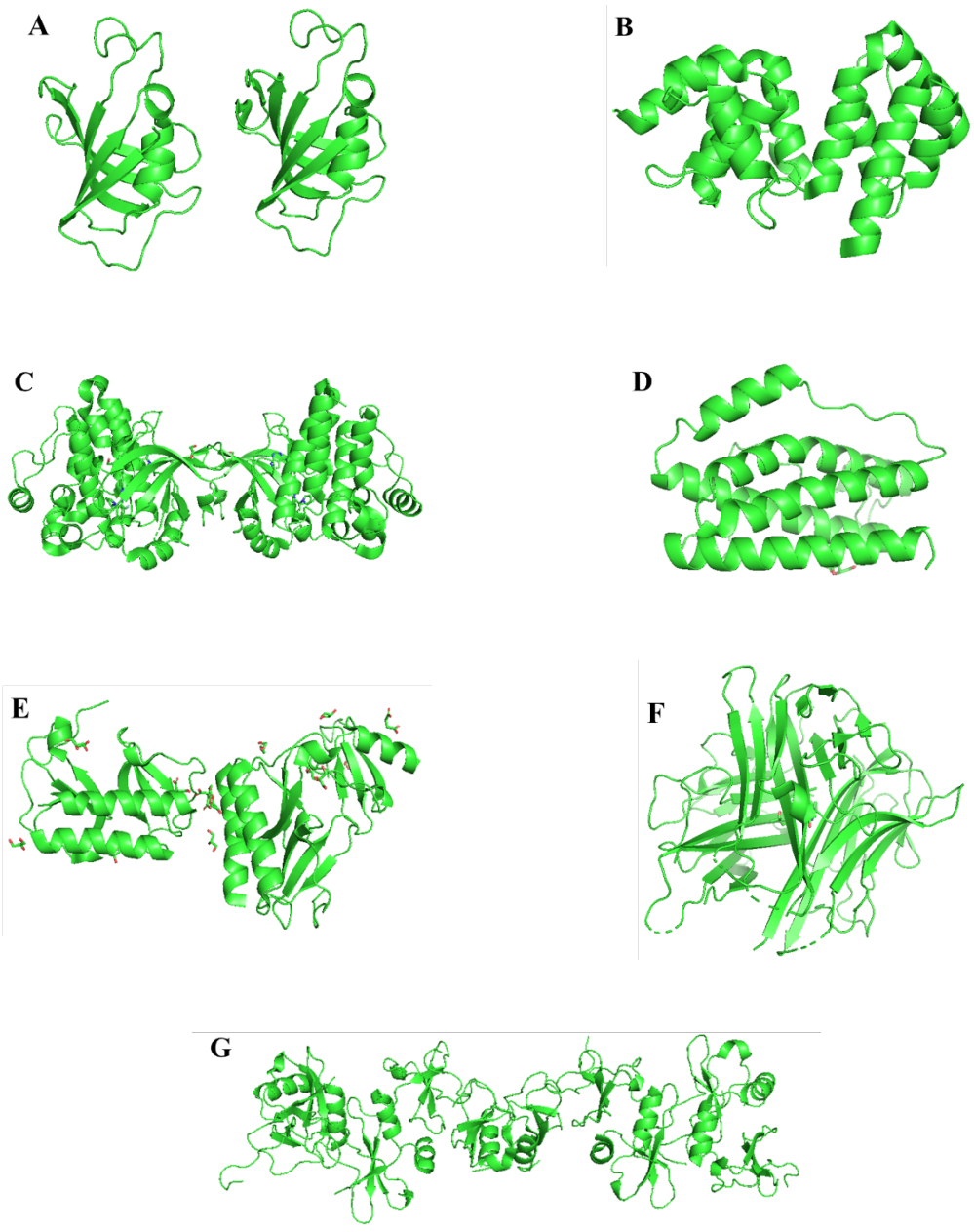

Figure 1. 3D structure of the proteins

A) FKBP1A (8X6P), B) CASP8 (7LVJ), C) BTK (6NZM), D) IL-6 (1ALU), E) CCL20 (7T1E), F) TNF-α (6OOY), G) CXCL12 (3HP3)

Abbreviations: FKBP1A: Peptidyl-prolyl cis-trans isomerase FKBP1A; CASP8: Caspase 8; BTK: Bruton tyrosine kinase; IL-6: Interleukin 6; CCL20: Chemokine (C-C motif) ligand 20; TNF-α: Tumour necrosis factor α.

Notes: The figures are visualized in PyMOL.

involved in the pathogenesis of RA [32-34]. Based on the published articles, we selected six proteins as receptor proteins for molecular docking: FKBP1A (8X6P), CASP8 (7LVJ), BTK (6NZM), IL-6 (1ALU), CCL20 (7T1E), CXCL12 (3HP3), and TNF-α (6OOY) (Figure 1). The protein structures were obtained from the Protein Data Bank. Then, the protein was imported into the PyMOL 2.5.7.0 tool [35]. PyMOL tool was used to eliminate heteroatoms, ligands, and water molecules from the protein. Lastly, the modified protein was saved in protein data bank format. Then, protein minimization was done by Swiss-PDBViewer 4.10 [36]. By this process, the proteins are prepared for molecular docking.

Molecular docking and visualization of the receptor-ligand interaction

The modified proteins were input into the PyRx 0.8 docking tool [37]. Then, the modified proteins were transformed into macromolecules. After that, the ligand molecules were imported into the PyRx 0.8. Then, the ligands were converted into PDBQT format. Consequently, they were turned into Autodock ligands. After that, proteins and ligands were selected, and the software was run. After that, the file containing the binding affinity of the ligands with the target molecule and the ligands was saved. The prepared combined structures were loaded into the Biovia Discovery Studio 21.1.0 tool, and the ligands and the receptors were defined individually [38]. Finally, the molecular interactions between the targeted protein and selected ligands were viewed and analyzed. In addition, 2D and 3D visualizations were performed.

Results

Absorption, distribution, metabolism, excretion and toxicity analysis

With the help of the Swiss-ADME server, we analyzed the ADME features of the selected compounds for anti-RA activity. Studied properties include molecular weight, number of rotatable bonds, number of H-bond acceptors, number of H-bond donors, lipophilicity (Log Po/w), water solubility (Log S -ESOL), gastrointestinal absorption, The blood-brain barrier permeant, Lipinski drug-likeliness properties, and synthesis feasibility. Analyzing a chemical substance's toxicity endpoints, including mutagenicity, carcinogenicity, and other characteristics, is one technique to quantify and assess a chemical substance's toxicity. The pkCSM server was used for the toxicity identification of a molecule, an essential stage in in-silico drug development. We studied properties like AMES toxicity, oral rat acute toxicity (LD_{50}), oral rat chronic toxicity (LOAEL), hepatotoxicity, and skin sensitization of the compounds. We also performed the total clearance of the compounds using the pkCSM server. The findings are shown in Table 2.

Molecular docking

The docking results of the selected compounds are shown in Table 3. The overall binding energy for all compounds was satisfactory. The binding energies range from -4.2 to -9.4. However, the highest docking score for bauchampine A was with BTK (-7.2 kcal/mol), betulinic acid with CCL20 (-8.8 kcal/mol), curcumol with TNF-α (-8.8 kcal/mol), geniposide with TNF-α (-8.7 kcal/mol), glycyrrhetinic acid with BTK (-9.4 kcal/mol), and paeoniflorin with BTK (-8.7 kcal/mol).

The ligand-receptor interactions of the highest scores are shown in Figure 2.

Bauchampine A is bound to FKBP1A, CASP8, BTK, IL-6, CCL20, CXCL12, and TNF-α by forming a conventional hydrogen bond with LYS(A:18) and ARG(A:19); ALA(A:155) and ARG(A:155); MET(A:477) and GLU(A:475); LYS(A:86), GLU(A:93), ASP(A:140) and ASN(A:63); ARG(E:13), LYS(D:44) and THR(D:41); GLN(E:63), GLN(E:59), ILE(B:28), and ASN(B:30); LYS(B:98), LYS(A:98), TYR(C:115) and SER(A:99), respectively. In addition, the carbonyl group formed a hydrogen bond with GLU(A:62), ALA(A:159) and LEU(A:149), MET(A:477), PRO(A:139), LYS(C:44) of FKBP1A, CASP8, BTK, IL-6, and CCL20, respectively. The other bonds between bauchampine A and the receptors include unfavorable donor, pi-alkyl, pi donor hydrogen bond, pi-pi stacked interaction, and pi anion interaction. The detailed interaction of the other ligands and receptors is compiled in Table 4.

Discussion

The hands and feet are the main areas affected by RA, a systemic poly-articular chronic inflammatory joint disease. Pathological manifestations of RA include pannus development, inflammatory cell infiltration, hyperplasia of the synovial membrane, and degeneration of the bone and cartilage in the joints. We studied six terpenoid compounds from Bangladeshi plants as potential candidates for anti-RA agents. The seven targets were selected as they have a profound role in RA's pathogenesis. Lipinski's criteria were supported by an analysis of the docked drugs' pharmacokinetics, which included examining their ADME characteristics. Toxicity tests were conducted on the substance to evaluate the chemical's possible harm to humans and animals.

ADME screening is necessary for a compound to meet the quality standards required to be considered a prospective drug candidate. A medicine candidate with a large molecular weight may have less permeability through a biological barrier. The lipophilicity of the target molecule is shown by the logarithm of its distribution coefficient among the hydrophilic and lipophilic phases. The log P indicates the degree to which the body captivates the drug. The degree to which the body absorbs a medicine is inversely correlated with its log P. Betulinic acid showed the highest log P (3.79) and bauchampine A possessed the lowest value (1.54). The log S value

Table 2. Pharmacokinetic and toxicity parameters of the selected compounds

Properties	Bauchampine A	Betulinic Acid	Curcumol	Geniposide	Glycyrrhetinic Acid	Paeoniflorin
Molecular weight (g/mol)	394.42	456.7	236.35	388.37	470.68	480.46
Rotatable bonds	4	2	1	6	1	7
H-bond acceptors	8	3	2	10	4	11
H-bond donors	6	2	1	5	2	5
Lipophilicity (Log Po/w)	1.45	3.79	2.31	2.22	3.54	1.57
Log S (ESOL) -3.02		-7.71	-3.02	-0.38	-6.15	-1.84
GI absorption	Low	Low	High	Low	High	Low
Blood-brain barrier permeant	No	No	Yes	No	No	No
Total clearance (log ml/min/kg)	0.344	0.116	0.975	1.404	-0.114	0.645
Lipinski drug-likeness, violation	Yes, 1	Yes, 1	Yes, 0	Yes, 0	Yes, 1	Yes, 1
Synthesis accessibility	4.37	5.63	5.52	5.8	6.08	5.51
AMES toxicity	No	No	No	No	No	No
Oral rat acute toxicity LD_{50} (mol/kg)	2.571	2.256	2.158	2.188	2.735	3.225
Oral rat chronic toxicity LOAEL (log mg/kg_bw/day)	3.63	2.206	1.848	3.087	1.664	4.196
Hepatotoxicity	No	Yes	No	No	No	No
Skin sensitization	No	34	Yes	No	No	No

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indicates the pharmaceutical candidate's solubility. The lowest log S value was found for betulinic acid (-7.71) and the highest value was shown by geniposide (-0.38). A drug's ability to function as both an acceptor and a donor of hydrogen bonds determines how easily it can pass through a cell membrane. Rotatable bond numbers enable bioavailability; the optimal range for these values

Table 3. Docking scores (binding affinity) of different phytoconstituents of anti-RA plants with FKBP1A, CASP8, BTK, IL-6, CCL 20, CXCL12, and TNF-α

Name of the Compounds	Binding Affinity (kcal/mol)						
	FKBP1A	CASP8	BTK	IL-6	CCL 20	CXCL12	TNF-α
Bauchampine A	-6.2	-6.9	-7.2	-6.5	-7	-7.1	-7.1
Betulinic acid	-7	-8.6	-8.3	-6.6	-8.8	-8	-4.2
Curcumol	-6.1	-6.2	-6.9	-5.9	-6.6	-6	-8.8
Geniposide	-5.8	-6.4	-8.2	-5.8	-7	-7.8	-8.7
Glycyrrhetinic acid	-7.6	-8.6	-9.4	-7.3	-7.8	-9.1	-8
Papeoniflorin	-6.8	-8	-8.7	-6.3	-7.8	-7.7	-8.1

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Abbreviations: RA: Rheumatoid arthritis; FKBP1A: Peptidyl-prolyl cis-trans isomerase FKBP1A; CASP8: Caspase 8; BTK: Bruton tyrosine kinase; IL-6: Interleukin 6; CCL20: Chemokine (C-C motif) ligand 20; TNF-α: Tumour necrosis factor α.

Table 4. Molecular interaction of the selected ligands with the receptors associated with RA

Receptor Protein	Molecules	Hydrogen Bond	Carbon Hydrogen Bond	Alkyl	Pi-Alkyl	Other Bonds
FKBP1A	Bauchampine A	LYS (A:18) ARG (A:19)	GLU (A:62)		ARG (A:19)	ARG (A:19) (Unfavorable Carbon Donor)
	Betulinic acid	ALA (A:65)		ALA (A:65) ARG (A:58) ARG (A:19)		
	Curcumol			VAL (A:56) ILE (A:57)	TYR (A:27) PHE (A:47) TRP (A:60)	
	Geniposide	GLN (A:54) GLY (A:52) ARG (A:58) ARG (A:19) LYS (A:18)	GLU (A:62) GLU (A:61)	ALA (A:65) LEU (A:51) ARG (A:19) LYS (A:18)		
	Glycyrrhetinic acid	LYS (A:18) ARG (A:19) GLN (A:54)		ALA (A:65)		
	Paeoniflorin	TYR (A:27)			PHE (A:37) PHE (A:100) TRP (A:60) TYR (A:27)	PHE (A:47) (Pi-pi T- shaped)
CASP8	Bauchampine A	ALA (A:155) ARG (A:155)	ALA (A:159) LEU (A:149)		PHE (A:240) ALA (A:155) ALA (A:159)	PHE (A:240) (Pi-pi Stacked)
	Betulinic acid	ARG (A:127)		ALA (A:155) ALA (A:159) VAL (A:162)	PHE (A:240)	
	Curcumol			ALA (A:159)	TYR (A:237) PHE (A:240)	
	Geniposide	TYR (A:165) VAL (A:171) SER (A:168)	VAL (A:171)	LEU (A:176) ARG (A:173)		
	Glycyrrhetinic acid		SER (A:158)	ARG (A:244) ALA (A:159) ALA (A:155)		
	Paeoniflorin	ILE (A:157) GLY (A:153) ALA (A:155) THR (A:151) ARG (A:127)	LEU (A:149) ALA (A:155)	VAL (A:162) ALA (A:159)		GLY (A:153) (Unfavorable Donor-Donor) PHE (A:240) (Pi-pi T- shaped)
BTK	Bauchampine A	MET (A:477) GLU (A:475)	MET (A:477)		VAL (A:416) LEU (A:528)	SER (A:538) MET (A:477) (Unfavorable Donor-Donor)
	Betulinic acid	PHE (A:413) GLY (A:414)	GLY (A:411) GLY (A:414)	VAL (A:416) LYS (A:430) LYS (A:558)	PHE (A:413) TYR (A:551)	
	Curcumol			ILE (A:397)	TRP (A:421) TYR (A:425) TYR (A:461)	TYR (A:461) (Pi sigma)
	Geniposide	TYR (A:551) ARG (A:525) ASP (A:521)	GLY (A:411) ASN (A:526) TYR (A:551)	LEU (A:542) LYS (A:430)	PHE (A:413)	PHE (A:413) (Pi donor hydrogen bond)
	Glycyrrhetinic acid	LYS (A:558) ARG (A:525)	PRO (A:560)	LYS (A:558)	TYR (A:551) TRP (A:563)	
	Paeoniflorin	MET (A:477)	ASP (A:539)	VAL (A:416) CYS (A:481) LEU (A:528)	LYS (A:430) LEU (A:542)	ASP (A:539) (Pi anion) MET (A:437) (Pi sulfur)

Receptor Protein	Molecules	Hydrogen Bond	Carbon Hydrogen Bond	Alkyl	Pi-Alkyl	Other Bonds
IL-6	Bauchampine A	LYS(A:86) GLU(A:93) ASP(A:140) ASN(A:63)	PRO(A:139)			GLU(A:93) (Pi anion)
	Betulinic acid			LYS(A:46) ARG(A:104)	PHE(A:105)	GLU(A:106) (unfavorable donor-donor)
	Curcumol				LEU(A:64) LEU(A:165) LYS(A:66) LEU(A:62)	
	Geniposide	ASP(A:140) ASN(A:63)	ASN(A:144) THR(A:143) LEU(A:147) SER(A:146)			
	Glycyrrhetinic acid	ARG(A:104) ASP(A:160) GLN(A:156)		LYS(A:46)	PHE(A:105)	
	Paeoniflorin	ARG(A:104) GLU(A:42) ASP(A:160)	PHE(A:105)	LYS(A:46)		
CCL20	Bauchampine A	ARG (E:13), LYS (D:44) THR (D:41)	LYS(C:44)		HIS (C:40) HIS (D:40)	
	Betulinic acid	THR (E:41)		LEU (E:15) VAL (E:47)		
	Curcumol	THR (E:41)		LEU (E:15) VAL (E:47)		
	Geniposide	ARG (E:13) ASP (D:5) LYS (C:44)	HIS (C:40) THR(C:41)		PHE(E:19)	SER(C:46) (unfavorable donor-donor) HIS D:40 (Pi sigma)
	Glycyrrhetinic acid	GLN (D:43) LYS (C:68) MET (C:70)		ARG (B:13) ILE (B:14) LYS (D:57)		
	Paeoniflorin	SER (D:46) THR (E:11)		LEU (D:45) LEU (E:15) VAL (E:47)		CYS(D:48) (unfavorable donor-donor)
CXCL12	Bauchampine A	GLN(E:63) GLN(E:59) ILE(B:28) ASN(B:30)				
	Betulinic acid	LYS(G:27) LYS(B:54)		LYS(B:56)	TRP(B:57)	
	Curcumol			VAL(I:23) LEU(I:26)	TYR(I:61)	
	Geniposide	ASN(E:30) ASN(G:30) ILE(G:28) GLU(I:63)	LEU(G:29) LEU(E:29)	LYS(E:27)	HIS(E:25)	
	Glycyrrhetinic acid	LYS(G:27) GLN(G:48) ASN(E:33)	LYS(B:56)	LEU(B:55)	HIS(G:25)	
	Paeoniflorin	LYS(G:27) ASN(E:30) SER(B:16) ASP(B:52) LYS(B:56)	LEU(B:55)	PRO(E:32) LYS(B:54)	LYS(B:56)	ASN(I:67) (Pi anion)

Receptor Protein	Molecules	Hydrogen Bond	Carbon Hydrogen Bond	Alkyl	Pi-Alkyl	Other Bonds
TNF- α	Bauchampine A	LYS(B:98) LYS(A:98) TYR(C:115) SER (A:99)				
	Betulinic acid	TYR(A:151) ILE(C:58)	TYR(A:119)	LEU(B:57) LEU(C:57) ILE(A:155)	TYR(C:119) TYR(B:59) TYR(B:119)	LEU (A:57) (unfavorable donor-donor)
	Curcumol	LEU(C:120)		LEU(A:57) LEU(C:57)	TYR(B:59) TYR(B:119) TYR(C:59) TYR(C:151)	
	Geniposide	GLY(B:12) TYR(B:119)	GLY(C:121) SER(A:60)		TYR(A:59) TYR(A:151) TYR(C:119)	
	Glycyrrhetinic acid	GLY(B:24)	GLU(B:23)	LEU(B:142) LYS(B:65)	PHE(B:144) TYR(B:141)	GLN(B:25) (unfavorable donor-donor)
	Paeoniflorin	TYR(C:115) LYS(B:98) LYS(A:98) LYS(C:112) GLU(A:116)	GLU(C:116)	LYS(A:98)		TYR(C:115) (unfavorable donor-donor) LYS (A:98) (Pi cation)

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Abbreviations: RA: Rheumatoid arthritis; FKBP1A: Peptidyl-prolyl cis-trans isomerase FKBP1A; CASP8: Caspase 8; BTK: Bruton tyrosine kinase; IL-6: Interleukin 6; CCL20: Chemokine (C-C motif) ligand 20; TNF-α: Tumour necrosis factor α.

lies within 10. All the compounds showed rotatable bond numbers within this limit.

A substance's toxicity is its capacity to cause harm to people or animals. Typically, animal models are employed to evaluate toxicity. This model is a lengthy and costly process. Because the in-silico method is inexpensive, short-lived, and does not need any animal object, it helps establish a compound's toxicity profile for drug development. The toxicological test servers (pkCSM) ascertain whether a medicine is carcinogenic. The studied compounds showed no toxicity in 'AMES toxicity' profiling; all were safe in hepatotoxicity testing except betulinic acid, and only curcumol showed a skin sensitization effect.

To help execute rational drug design, molecular docking techniques can be utilized to determine the binding affinities of different ligands for the target protein structure. This method can help comprehend the dynamics of interactions and possible binding mechanisms, which can be used to apply more stringent inhibition [39]. The docking scores of these compounds revealed excellent binding properties with the targets. Individual compounds have distinct binding affinity with different targets. The BTK has the highest scores for the compounds. The bonds among the compounds and the receptors are also diverse.

BTK plays a vital role in mononuclear cells of the innate immune system, especially in dendritic cells and macrophages. Moreover, it is a direct regulator of the NLRP3 inflammasome, a key innate inflammatory machinery [40]. Studies revealed that inhibition of BTK resulted in the downregulation of B cells and thus reduced RA-mediated inflammation [41, 42]. In our study, bauchampine A, glycyrrhetinic acid, and papeoniflorin showed the most significant binding affinity with BTK. These compounds have a selective affinity to BTK, which can be used to inhibit the protein. There is growing interest in inhibiting BTK for anti-RA medication development [43], so these compounds may serve as potential candidates.

Another crucial inflammatory cytokine in this study is TNF-α. Excessive upregulation of TNF-α is associated with chronic inflammation that can result in autoimmune diseases [44, 45]. Blocking the destructive activity of TNF has been used in the treatment of RA for several years [46, 47]. Curcumol and geniposide showed the highest binding energy score with TNF-α, which is also promising for blocking this pathway [48, 49].

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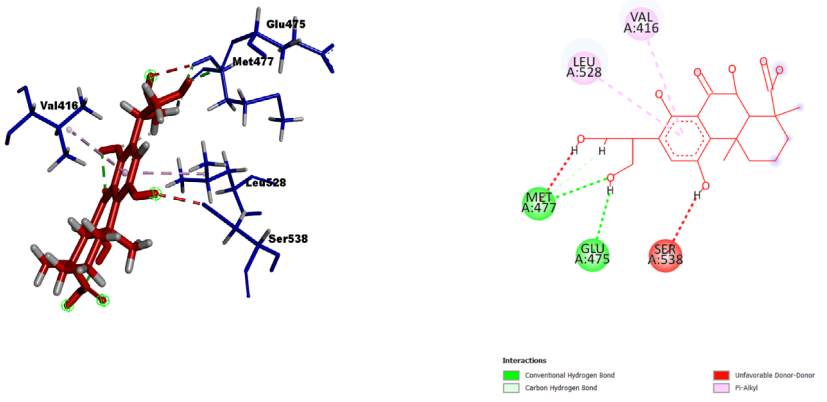
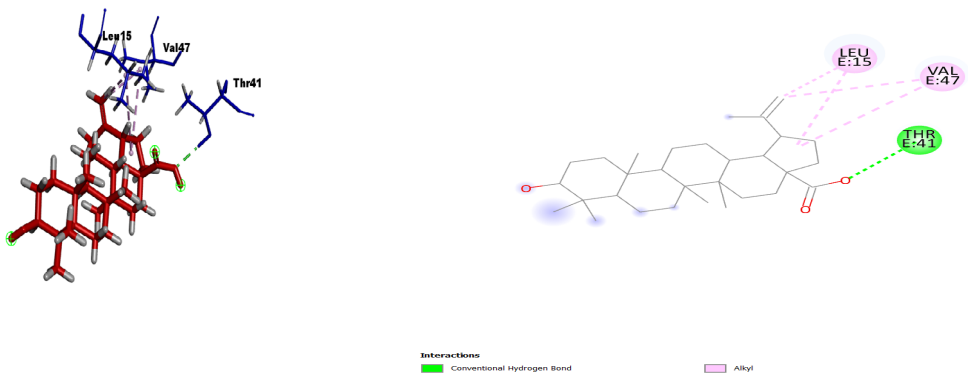
3D interaction

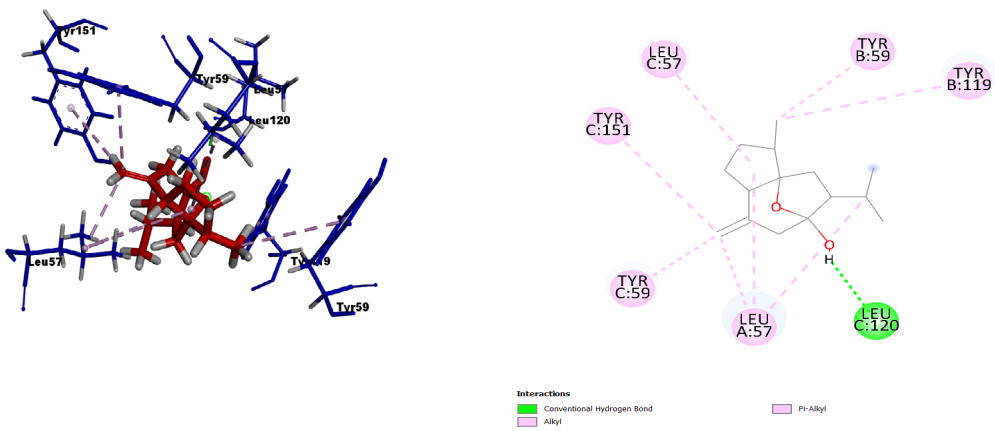
2D interaction



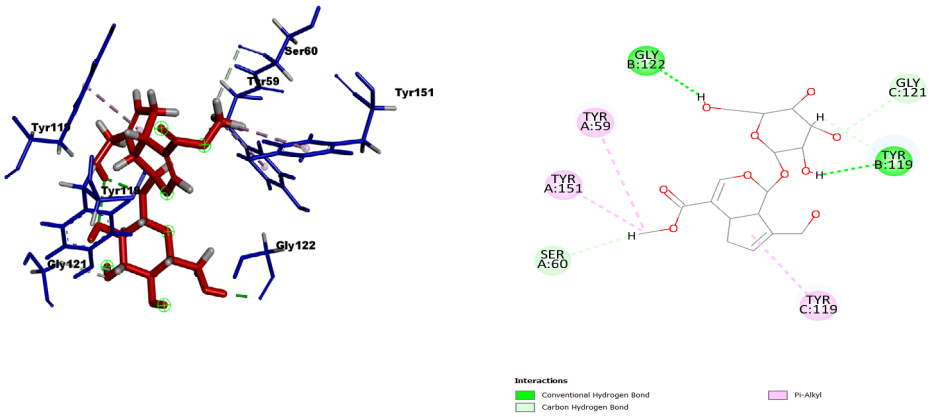
A) Bauchampine a with BTK



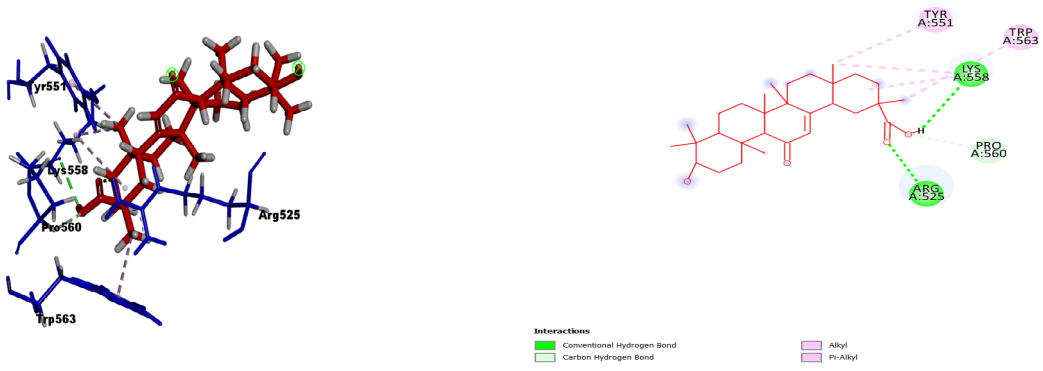
B) Betulinic acid with chemokine (C-C motif) ligand 20



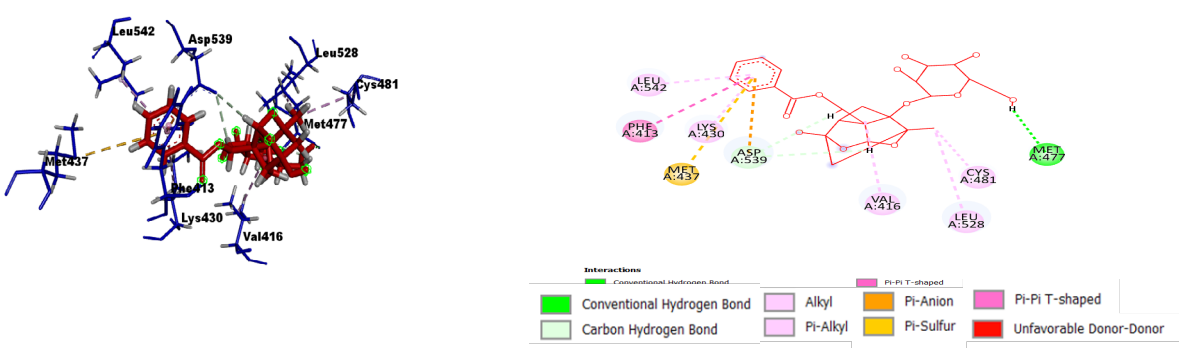
C) Curcumol with tumor necrosis factor-α



D) Geniposide with tumor necrosis factor-α



E) Glycyrrhetinic acid with BTK



F) Papeoniflorin with BTK

Figure 2. The 3D and 2D diagram of ligand-receptor interactions

A) Bauchampine A and BTK, B) Betulinic acid and chemokine (C-C motif) ligand 20, C) Curcumol and tumor necrosis factor-α, D) Geniposide and tumor necrosis factor-α, E) Glycyrrhetinic acid and BTK, F) Papeoniflorin and BTK

The chemokines are actively involved in inflammatory disorders, and CCL20 is a vital chemokine [50]. The binding energy of betulinic acid with CCL20 was the highest. The role of CCL20 in the pathogenesis of RA is unclear, though the patients contain higher levels of the chemokine than healthy individuals [51, 52]. The compound has the most affinity to the chemokine than other proteins.

Conclusion

Plant-derived terpenoid compounds can serve as effective leads for developing anti-RA medications. In this study, terpenoid molecules were tested against several proteins engaged in RA pathogenesis. This study revealed the tested compounds' binding site and affinity for their targets. The compounds showed significant binding scores with different receptor proteins. Glycyrrhetinic acid showed the highest binding scores with BTK. The pharmacokinetic properties were also evaluated to confirm their drug-likeness. Almost every compound showed potential drug-like pharmacokinetic parameters. The toxicity profiling of the terpenoids also showed auspicious results. The present study may aid the development of effective drugs for rheumatic arthritis.

Limitations

The computational approaches used in this study have several limitations that impact their effectiveness. In this study, the accuracy of predictions is often constrained by simplified models that may not fully capture complex molecular interactions or the dynamic nature of biological systems. Additionally, predicting critical drug properties like absorption, distribution, metabolism, excretion, and toxicity remains challenging and prone to errors. Moreover, the results from in silico studies require experimental validation, which can reveal discrepancies and unforeseen issues, such as drug-drug interactions or off-target effects, that were not predicted. Further in-depth research, as well as in vitro and in vivo investigations, should be conducted to get above the study's constraints and enhance the computational techniques employed.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and supervision: Md Monirul Islam; Methodology: Iqbal Mahmud, and Md Habibur Rahaman; Data analysis: Md Monirul Islam, and Iqbal Mahmud; Investigation and writing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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