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Original Article

Computational Profile of Novel Natural Bioactive Inhibitors of NF-κB

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ABSTRACT

Nuclear factor-κB (NF-κB) represents a family of inducible transcription factors, that regulates a large array of genes involved in different processes of the immune and inflammatory responses. Deregulated NF-κB activation contributes to the pathogenic process of various diseases such as inflammation and cancer. NF-κB signaling in cancer cells is involved in cellular proliferation, angiogenesis, invasion, metastasis, development of drug resistance and anti-apoptosis. **Objective:** To identify potent NF-κB and IκBα inhibitors using molecular docking study. **Methods:** Proteins and ligands were prepared from Pymol and AutoDock vina and results were visualized by using Discovery studio visualizer. **Results:** Natural bioactive compounds such as Brevilin A, Tagitinin E, Japonicone G and Hiyodorilactone A were targeted on NF-κB and IκBα. The docking score of the Brevilin A, Tagitinin E, Japonicone G and Hiyodorilactone A with NF-κB were -9.8Kcal/mol, -10.1Kcal/mol, -11.9Kcal/mol, and - 8.4Kcal/mol respectively. The docking score of the Brevilin A, Tagitinin E, Japonicone G and Hiyodorilactone A with IκBα were -7.1Kcal/mol, -7.0Kcal/mol, -8.8Kcal/mol and -6.8Kcal/mol respectively. Control group (JSH-23 synthetic inhibitor) showed -6.5Kcal/mol and -5.5Kcal/mol with NF-κB and IκBα respectively. **Conclusions:** The present study reflects that Brevilin A, Tagitinin E, Japonicone G and Hiyodorilactone A show promising results as a crucial drug target in NF-κB signaling cascade. However, to validate the inhibitory activity of these ligands further *in-vitro* analysis is suggested to develop novel anti-inflammatory/anti-cancer drugs.

INTRODUCTION

The NF-κB is the transcriptional factor that plays a vital role in oncogenesis, embryonic development, innate, adaptive immunity, cell differentiation, cell adhesions, apoptosis, metastasis, angiogenesis, and oxidative stress [1]. Mainly, NF-κB consists of 5 proteins: p65/Rel A, Rel B, C-Rel, p50, and p52 that can homo or hetero dimerize to 15 different NF-κB complexes [2,3]. The most common pathway of NF-κB activation is the canonical pathway [4]. In the classical pathway, NF-κB is inactive in the cytosol, bound to inhibitory proteins. Phosphorylation, ubiquitination, and degradation of these inhibitors activate NF-κB. This active form translocates to the nucleus, binds to DNA, activates target genes, and influences cell proliferation and apoptosis [5]. In the alternative pathway, p52/RelB is activated by NIK, which plays a key role. NIK processes signals from the TNF-α family, activating IKK-α, leading to p100 conversion into p52. This complex activates distinct genes, and deregulation can cause osteoporosis and autoimmune diseases [6]. Cancer and inflammation are mainly caused by the deregulation of NF-κB [7]. NF-κB in cancer cells is involved in metastasis, proliferation, angiogenesis, and invasion and prevents apoptosis [3]. NF-κB has multiple points of regulation, which recently became a target for many therapeutic drugs. Prime targets to develop NF-κB inhibitors are either directly bound to the IKK complex; Nuclear translocation of NF-κB, NF-κB directed gene transactivation, Phosphorylation, ubiquitination, proteasomal degradation of IκB and NF-κB

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binding to DNA [8]. Non-steroidal anti-inflammatory drugs like ibuprofen, indomethacin, and aspirin can stop the NF-κB activation [9, 10]. The natural bioactive compound has been a significant source of drugs in the medical field. From natural sources, several commercialized drugs have been obtained for the treatment of cancer. In cancer chemotherapeutics, natural compounds have a central role and 60% of anticancer compounds are natural products or derivatives of natural products [11].

The present study was designed to explore the potential of natural bioactive compounds such as Brevilin A, Tagitinin E, Japonicone G, and hiyodorilactone A as a therapeutic agent in the NF-κB signaling pathway by employing various bioinformatics tools. Various aspects of the compounds were evaluated by molecular docking study and their anticancer and anti-inflammatory role was assessed in-silico.

METHODS

To evaluate the in-silico potential inhibitory effect of natural bioactive compounds on NF-κB and IκBα, receptors and ligands were docked by using Autodock vina [12]. Before executing the docking, protein, and ligands were prepared in PDBQT file format by using various bioinformatics tools.

Preparation of Protein

Crystal structure of proteins NF-κB (PDB ID: 1VKX) and IκBα (PDB ID: 1NFI) were retrieved from PDB in PDB file format [11, 13, 14]. Proteins were prepared by AutoDock MGL Tools 1.5.6 and the process of preparation involved the deletion of water, by adding polar Hydrogen and inserting Kollman charges. Finally, the proteins were saved in PDBQT file format (Figure 1).

Ligand Preparation

Ligand structures of Brevilin A, Tagitinin E, Hiyodorilactone A, and Japonicone G were obtained from the PubChem in sdf format and converted into PDB format using pymol and subsequently by Autodock vina, into PDBQT (Figure 2) [15].

Docking

The molecular docking analysis was performed using exhaustiveness value (8) and the grid box was prepared using "40 points in three dimensions X, Y and Z with center_x = 0.592, center_y = 30.925 center_z = 56.581 with NF-κB and center_x = -5.372 center_y = 65.520 center_z = 45.295 with IκBα with the spacing of 0.375Å. Receptors were treated as inflexible target while ligand was kept flexible. Docking was executed by using MGL Tools (Autodock 1.5.6) [16]. The results of visualization were determined by using BIOVIA Discovery Studio Visualizer [17].

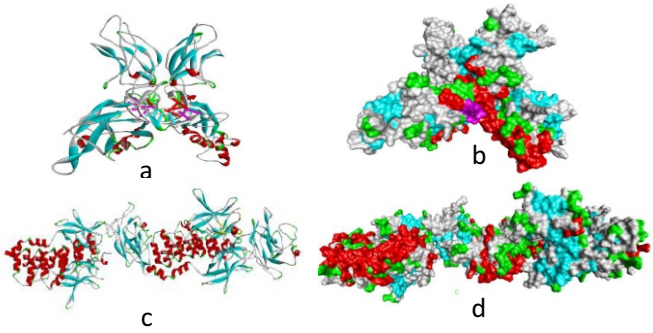

Figure 1: a) Ribbon structure of NF-κB b) Surface structure of NF-κB c) Ribbon structure of IκBα d) Surface structure of IκBα.

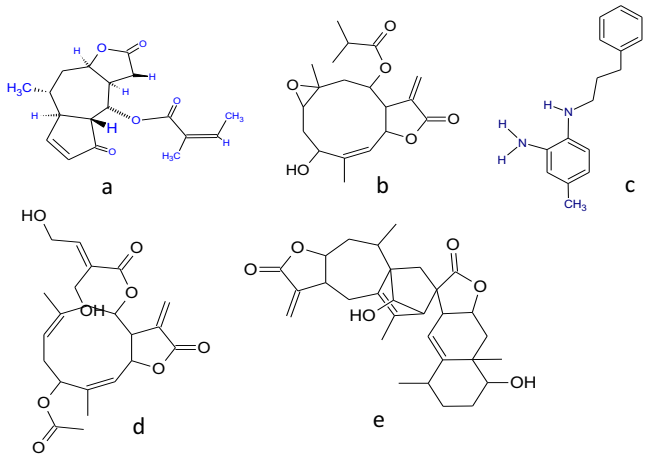

Figure 2: Chemical structure of various bioactive ligands. a) Brevilin A b) Tagitinin E c) JSH-23 d) Hiyodorilactone A e) Japonicone G

ADME/T and Drug likeness

ADME abbreviated as "absorption, distribution, metabolism, and excretion", is important in predicting the pharmacokinetics of the proposed drug candidate which improves its chances as a successful drug. SWISS-ADME is an online server that allows drawing the respective drug structure or adding canonical SMILES obtained from PubChem [18]. This software was used to compute ADME, drug-like nature, and pharmacokinetic properties of studied ligands [19]. It is also an online database, used for toxicity analysis, which gives the toxicity results of any molecule in terms of Hepatotoxicity, T. pyriformis and Minnow toxicity, maximum human tolerance dose, AMES Toxicity, Skin Toxicity, and Ld50.

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RESULTS

The ligands were docked, and their in-silico activities were evaluated. ADME analysis revealed that Brevilin A, Tagitinin E, Hiyodorilactone A and Japonicone G have a molecular weight in the range of 346g/mol, 350g/mol, 420g/mol, and 494g/mol respectively (Table 1).

Table 1: Drug likeness profile of various ligands

Parameters	Brevilin A	Tagitinin E	Hiyodori-lactone A	Japoni-cone G
Molecular Formula	$C_{20}H_{26}O_5$	$C_{19}H_{26}O_6$	$C_{22}H_{28}O_8$	$C_{30}H_{38}O_6$
Consensus Log Po/w	2.62	2.09	1.61	3.50
Water Solubility	-3.24	-2.9	-2.36	-4.60
GI-Absorption	High	High	High	High
Log Kp (skin-permeation)	-6.78 cm/s	-7.21 cm/s	-8.45 cm/s	-7.41 cm/s
Veber rule	Yes	Yes	Yes	Yes
Lead likeness	Yes	No	No	No
Synthetic accessibility	5.13	5.61	5.66	7.68

Toxicity analysis results predict that all ligands have no hepatotoxicity and no skin sensation except Japonicone G which showed hepatotoxicity. Tagitinin E showed AMES toxicity while all the other studied ligands did not. All the results of the ADME profile and toxicity prediction are shown in table 2.

Table 2: Toxicity prediction of various ligands

Ligand	Brevilin A	Tagitinin E	Hiyodori-lactone A	Japoni-cone G
AMES toxicity	No	Yes	No	No
Maximum tolerated dose (human) (log mg/kg/day)	-0.081	-0.007	-0.163	-0.813
Oral rat acute toxicity (mol/kg)	2.158	3.019	2.427	2.241
Oral rat chronic toxicity (log mg/kg bw/day)	1.133	1.788	2.06	1.653
Hepatotoxicity	No	No	No	Yes
Skin sensation	No	No	No	No
T. pyriformis toxicity (log ug/L)	0.495	0.393	0.276	0.289
Minnow toxicity (log mM)	1.951	2.554	4.069	1.555

The analysis of ligands on Lipinski Rule of 5 shown in table 3.

Table 3: Analysis of ligands on Lipinski Rule of 5

Ligands	Mass	H-bond Donor	H-bond acceptor	LOGP	Molar refractivity	Ro5 violation
Brevilin A	346	0	5	2.84	91.36	0
Tagitinin E	350	1	6	1.91	89.50	0
Japonicone G	494	2	6	3.87	131.16	1
Hiyodorilactone A	420	2	8	1.53	106.95	0

The Representation of various ligands following Lipinski Rule of 5 shown in figure 3.

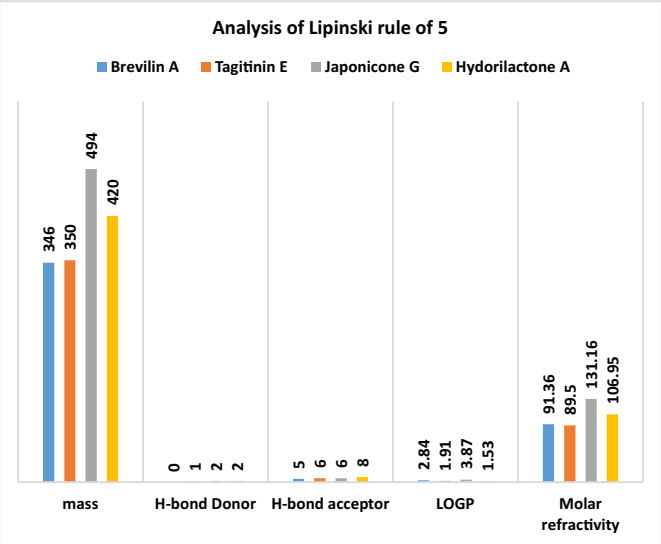

Figure 3: Representation of various ligands following Lipinski Rule of 5

Molecular Docking (MD)

MD results revealed that the selected ligands are potential inhibitors of NF-κB and IκBα. The MD analysis was performed in triplicate to get a valid assessment of the mode of interaction of ligands against selected proteins. For each ligand, 9 different poses were generated and the one that was selected contained less energy and more interactions. The NF-κB crystal structure contains 2 chains, p50 and p65 that were attached with DNA, while IκBα contains two chains, A and C. The ligands may bind with given chains of target protein upon the susceptibility of the atom for specific interaction. The binding energy values are given in (Table 4 and Figure 4).

Table 4: Binding affinity values of various ligands with NF-κB and IκBα

Ligand	NF-κB	IκBα
Tagitinin E	-10.1Kcal/mol	-7.0Kcal/mol
Brevilin A	-9.8Kcal/mol	-7.1Kcal/mol
Hiyodorilactone A	-8.4Kcal/mol	-6.8kcal/mol
Japonicone G	-11.9Kcal/mol	-8.8Kcal/mol
JSH-23	-6.5Kcal/mol	-5.5Kcal/mol

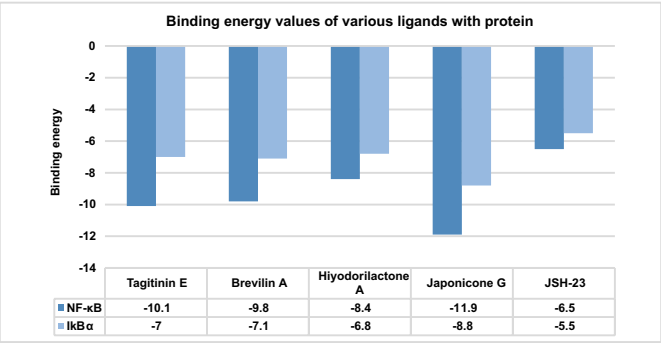

Figure 3: Binding affinity of various ligands

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Low binding energy means more stable will be the ligand-receptor complex. The selected ligands were compared with JSH-23 (synthetic inhibitor) and found that they had lower binding values and more interactions hence the natural inhibitors are more potent than synthetic ones. The docking results revealed that Brevilin A, Hiyodorilactone A, Japonicone G, and Tagitinin E successfully bind in the binding pocket of NF-κB and IκBα. Brevilin A strongly interacts with the binding pocket of NF-κB DNA complex, and it has a binding energy of -9.8kcal/mol with NF-κB and forms H-bonding with DC7 (2.25Å), DA16 (2.21Å), DA17 (2.61Å), DA18 (2.93Å) and no hydrophobic and electrostatic interactions. Whereas it has a binding energy of -7.1kcal/mol with IκBα and forms H-bonding but forms no hydrophobic and electrostatic interactions. The interaction of other ligands with the amino acid residues of the targeted proteins is shown in figure 5-11 and table 5.

Table 5: H-bonding, Hydrophobic interaction of various ligands with proteins

Ligands/ Inhibitors	NF-κB		IκBα	
	H-Bonding	Hydrophobic	H-Bonding	Hydrophobic
Brevilin A	DC7(2.25Å) DA16(2.21Å) DA17(2.61Å) DA18(2.93Å)	-	ARG73(2.76Å) GLN142(2.42Å)	-
Tagitinin E	DA17(2.44Å) DA18(2.64Å) DA16(3.62Å) ARG605(2.37Å) GLN606(2.22Å)	LYS218(4.88Å) ARG187 (4.17Å)	ARG95 (2.69 Å)	-
Japonicone G	DA6(2.49Å) LYS572(1.83Å) GLN606(2.17Å) DG19 (2.26Å)	DA6(3.63Å)	ASN137 (2.32Å) PRO172 (2.18Å)	ARG174 (4.77Å)
Hiyodoril-actone A	LYS218(2.41Å) ARG605(2.44Å) ASN186(2.21Å) DA16(4.88Å) DA17 (4.74Å)	-	GLN142(2.94Å) THR164(2.46Å) ARG95(2.15Å) THR164(2.55Å) GLN162(3.54Å) LEU175(3.56Å)	MET91(5.14Å) ARG95(3.88Å)
JSH-23	DT8 (2.48Å)	ARG246(4.51Å) DA16(4.16Å) PHE607(4.74Å) LYS218(5.38Å) ARG605(4.39Å)	LEU175 (2.32Å) ARG174 (2.02Å)	GLN162(5.18Å) VAL163(5.18Å) ARG174(4.37Å) PRO177(5.40Å)

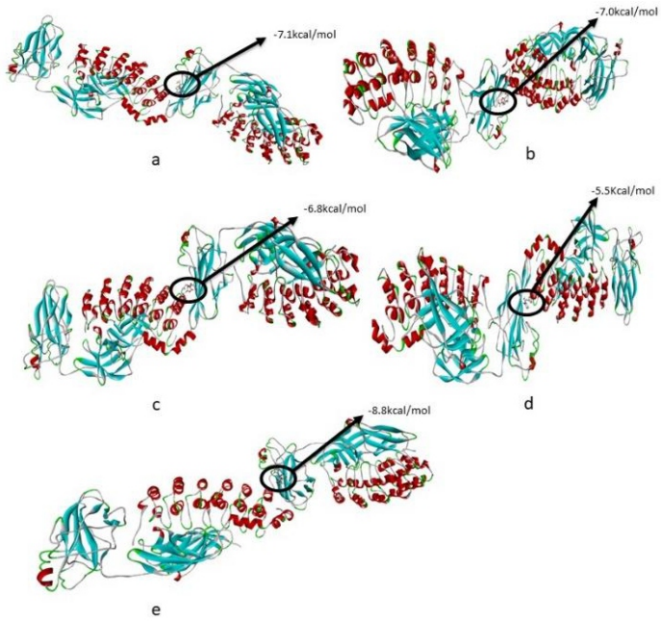

Figure 5: Binding of different compounds on different binding site of IκBα. a) Brevilin A-IκBα b) Tagitinin E-IκBα c) Hiyodorilactone A-IκBα d) JSH-23-IκBα e) Japonicone G-IκBα

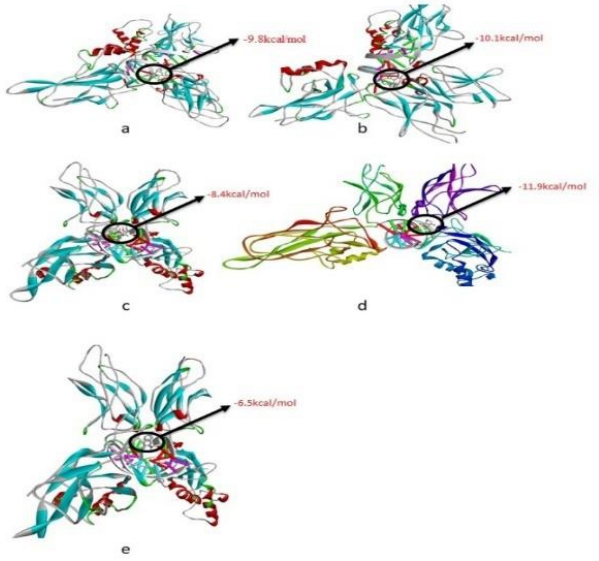

Figure 6: Binding of selected ligands on different binding sites of NF-κB. a) Brevilin A-NF-κB b) Tagitinin E-NF-κB c) Hiyodorilactone A-NF-κB d) Japonicone G-NF-κB e) JSH-23-NF-κB.

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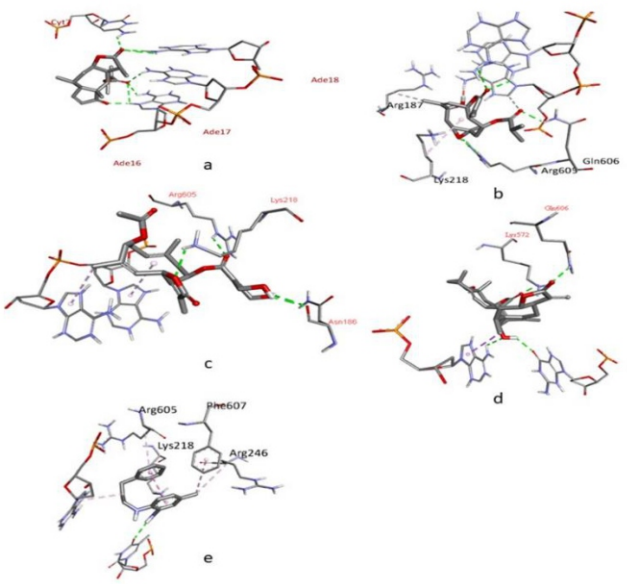

Figure 7: Interaction of ligands with the amino acid residues of NF-κB (Sticks model). Black color sticks represent the ligand while green dotted lines show Hydrogen bonds. a) Brevilin A-NF-κB Complex b) Tagitinin E-NF-κB Complex c) Hiyodorilactone A-NF-κB Complex d) Japonicone G-NF-κB Complex e)JSH-23-NF-κB Complex

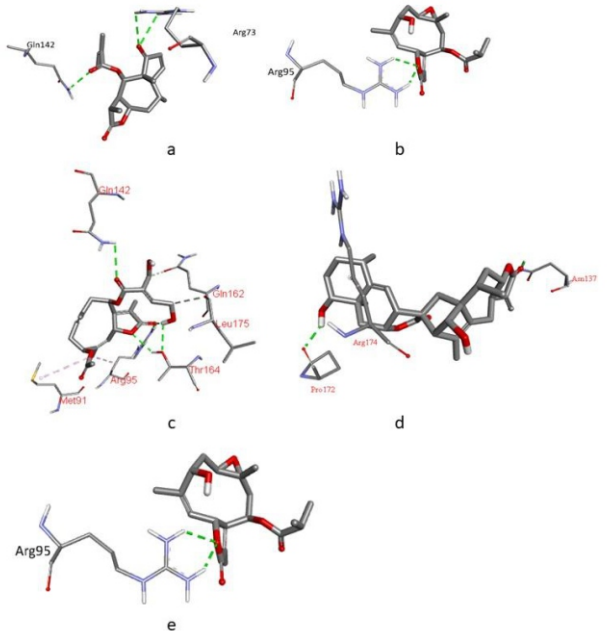

Figure 8: Interaction of various ligands with the amino acid residues of IκBα (Sticks model). Black color sticks represent the ligand while green dotted lines show Hydrogen bonds. a) Brevilin A-IκBα Complex b) Tagitinin E-IκBα Complex c) Hiyodorilactone A-IκBα Complex d) JSH-23-IκBα Complex e)Japonicone G-IκBα Complex

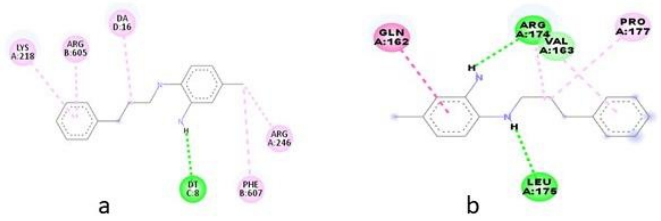

Figure 9: 2-D Diagrams of JSH-23 with both proteins. Green dotted lines represent the hydrogen bonds interaction while pink and light pink dotted lines show the hydrophobic interaction of amino acids residues with ligand. a) JSH-23 interaction with NF-κB b) JSH-23 interactions with IκBα

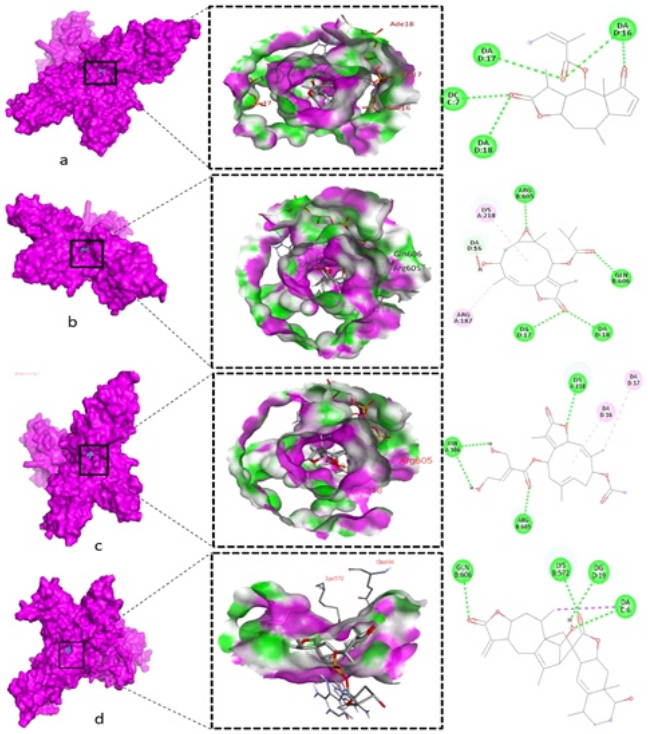

Figure 10: Docking of selected ligands into NF-κB. Total density surface (TDS) as represented with H-bond donor and acceptor moieties with pink and green mesh colors in 2-D diagram. a) Brevilin A b)Tagitinin E c) Hiyodorilactone A d) Japonicone G. Green dotted lines shows the hydrogen bonds while pink dotted lines shows the hydrophobic interaction of amino acids residues with ligands

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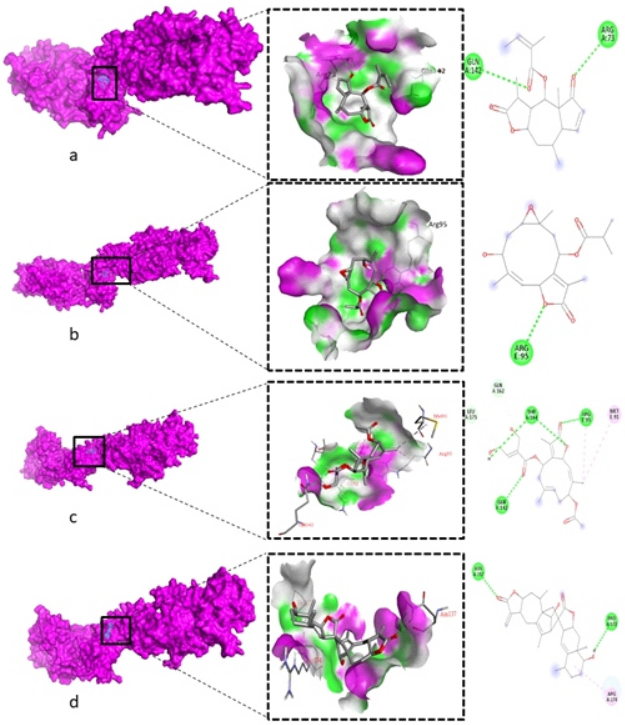

Figure 11: Docking of selected ligands into IκB-α pocket. TDS as represented with H-bond donor and acceptor moieties with pink and green mesh colors in 2-D diagram. a) Brevilin A b) Tagitinin E c) Hiyodorilactone A d) Japonicone G. Green dotted lines show the hydrogen bonds while pink dotted lines show the hydrophobic interaction of amino acids residues with ligands

DISCUSSION

The results of the present study revealed that Japonicone G, Tagitinin E, and Brevilin A are promising inhibitors of NF-κB complex, considering them the best target for drug development. The selected ligands mainly targeted NF-κB DNA complex and NF-κB dimer with IκBα. A similar study was reported by Savitri et al. who also targeted the NF-κB DNA complex and identified novel bioactive compounds from kepok banana peels [20]. The present investigation revealed that all the selected ligands potentially interact with the residues of NF-κB and IκBα and proved as its promising inhibitors. The binding energy values obtained from the interaction of Brevilin A, Tagitinin E, Hiyodorilactone A, and Japonicone G with NF-κB and IκBα were significantly less than the binding energy of JSH-23 (synthetic inhibitor), thus making these natural compounds, the most promising inhibitors. The following is the binding energy order of studied ligand-protein complexes: Japonicone G<Tagitinin E< Brevilin A< Hiyodorilactone A<JSH-23. Thus, in the present study, the most stable ligand-protein complex was Japonicone G-NF-κB DNA complex, Tagitinin E – NF-κB DNA complex, and Brevilin A-NF-κB DNA complex. Kadioglu et al., presented a similar study in which Kaempferol (natural compound) was docked against NF-κB DNA complex [21]. The binding energy of Kaempferol against the NF-κB DNA complex was -10.25kcal/mol. In another investigation, the activity of a natural bioactive compound, DHMA against NF-κB DNA complex and its binding energy was -6.6kcal/mol [22]. Shrivastava et al., reported that Resveratrol and Piperlongumine have a binding energy of -3.96kcal/mol, and -3.28kcal/mol against NF-κB respectively [23]. Another study showed that natural compounds similar to our study, exhibited good binding energy value and can be used in the place of synthetic inhibitors [24, 25]. Bioactive compounds Japonicone G, Hiyodorilactone A, Brevilin A Tagitinin E, and JSH-23 make different types of interactions like hydrogen and hydrophobic bonding by targeting several binding residues at different active sites. The role of H-bonding in the receptor-ligand complex is very crucial because H-bonding is involved in the secondary structure of proteins such as α-helix and β-plated sheets. It is also important for the binding affinity of ligands. Ligand binding with receptors is significantly determined by several intermolecular H-bonds. In H-bonding, short bond distance means strong interaction between receptor-ligand. In this study, Japonicone G, Hiyodorilactone A, Brevilin A and Tagitinin E interacts with NF-κB via hydrogen bond with DA6, LYS572, DG19, LYS218, ASN186, DA16, DA17, DC7, DA18, ARG605 and GLN606 and hydrophobic interaction at LYS218, ARG187 and DA6. Japonicone G, Hiyodorilactone A, Brevilin A, and Tagitinin E interact with IκBα via H-bond interaction with ASN137, PRO172, THR164, GLN162, LEU175, ARG73, GLN142 and ARG95 and hydrophobic interaction at MET91, ARG95 and ARG174. While JSH-23 interacts with NF-κB DNA complex via different interactions such as hydrophobic interaction with ARG246, DA16, PHE607, LYS218 and ARG605 and hydrogen bond with DT8. JSH-23 interacts with IκBα via different interactions like H-bond interaction with LEU175 and ARG174 while hydrophobic interaction with GLN162, VAL163, ARG174, and PRO177. These interactions make them a perfect fit as drug inhibitors. Savitri et al., reported that trigonelline, 3-methoxyfavone, and salsolinol formed H-bond interactions with Lys123 Tyr152 and Asp153 whereas isovanillic acid formed H-bond with Arg84 [20]. Similarly, in our study, Brevilin A formed an H-bond with Arg95. Ren et al reported that Aureusidin forms H-bonding with Arg35, Ala43, Ser42, Ser42, and Arg41 residue of NF-κB [26]. It was shown that DHMA forms H-bond interactions with DNA like DG-3, DG-4, and DG-5 residues of the NF-κB DNA complex. Our inhibitors bind with DA6, DA17 and DA18, DC7, DT10 and DT20 [22]. The pharmacokinetic properties easily predict the acquiescence of potential natural

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compounds and equivalents compared with that of the standard drug. Currently, the oral bioavailability of any FDA-approved drug or inhibitor and its tolerable distribution into the human body is a critical issue [27]. ADME analysis showed that Brevilin A, Tagitinin E, Hiyodorilactone A and Japonicone G have molecular weight in the range of 346.2g/mol to 494.62g/mol and Molar refractivity range from 91.01 to 134.22; values of lipophilicity, consensus (Log Po/w), water solubility, LogKp and synthetic accessibility range from 2.84-3.87, 2.62-3.50, -3.24 to -4.60, -6.87cm/s to -8.45cm/s and 5.13 to 7.68 respectively. Moreover, the selected ligands are highly absorbed by the GI, and they follow the Lipinski rule and drug-likeness. Our compounds exhibit favorable drug-like properties, moderate toxicity levels well within acceptable limits, and compliance with Lipinski's rule. These characteristics make them promising candidates for future in-vivo, in-vitro, and clinical trial studies [28].

CONCLUSIONS

The present study reveals that bioactive natural compounds, japonicone G, Tagitinin E, Hiyodorilactone A, and Brevilin A have good binding affinity with NF-κB and IκBα. They form multiple interactions like H-bonding, hydrophobic, and electrostatic interaction with NF-κB and IκBα. Their comparison with standard synthetic inhibitor JSH-23 shows that these natural compounds interact more strongly than JSH-23 with target proteins. Based on the current in-silico study, Tagitinin E and Brevilin A have emerged as anti-inflammatory and anticancer compounds in the therapeutic research which need in-vitro and in-vivo trials for therapeutic use.

Authors Contribution

Conceptualization: MM, MK
Methodology: MI
Formal analysis: MI, MFM
Writing-review and editing: MI, MFM, AS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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