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Anti-inflammatory Activity of *Sambucus* Plant Bioactive Compounds against TNF-α and TRAIL as Solution to Overcome Inflammation Associated Diseases: The Insight from Bioinformatics Study

Wira Eka Putra[1], Wa Ode Salma[2], Muhaimin Rifa'i[3,*]

[1]*Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, Indonesia*
[2]*Department of Nutrition, Faculty of Medicine, Halu Oleo University, Indonesia*
[3]*Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Indonesia*

Abstract – Inflammation is the crucial biological process of immune system which acts as body's defense and protective response against the injuries or infection. However, the systemic inflammation devotes the adverse effects such as multiple inflammation associated diseases. One of the best ways to treat this entity is by blocking the tumor necrosis factor alpha (TNF-α) and TNF-related apoptosis-inducing ligand (TRAIL) to avoid the pro-inflammation cytokines production. Thus, this study aims to evaluate the potency of *Sambucus* bioactive compounds as anti-inflammation through *in silico* approach. In order to assess that, molecular docking was performed to evaluate the interaction properties between the TNF-α or TRAIL with the ligands. The 2D structure of ligands were retrieved online via PubChem and the 3D protein modeling was done by using SWISS Model. The prediction results of the study showed that caffeic acid (-6.4 kcal/mol) and homovanillic acid (-6.6 kcal/mol) have the greatest binding affinity against the TNF-α and TRAIL respectively. This evidence suggests that caffeic acid and homovanillic acid may potent as anti-inflammatory agent against the inflammation associated diseases. Finally, this study needs further examination and evaluation to validate the potency of *Sambucus* bioactive compounds.
Keywords – Bioinformatics study, inflammation, *Sambucus*, TNF-α, TRAIL

Introduction

Inflammation is the metabolic condition that caused by various factors covering inflammatory inducers, sensors, and mediators.[1] One of the most common term classically defined inflammation as the immunological response to the infection or injury.[2] Generally, the inflammation signal activated under the intruder attack or tissue damage. The inflammation characterized by redness, swelling, heat, pain, and loss of tissue function.[3] This condition commonly followed by certain pathological condition like the production of pro-inflammatory cytokines such as TNF-α and IL-1β.[4] However, the excessive amount of inflammatory mediators in chronic inflammation lead to adverse effect called inflammation related diseases such as obesity, cardiovascular, neurodegenerative diseases and cancer.[5-10]

Based on the severity level, the inflammation are divided into two types, acute and chronic inflammation.[11] During the acute inflammation condition, the cellular and molecular of biological activities attempts to suppress the negative effect of inflammation. But, ironically uncontrolled acute inflammation leads to the worst effect called chronic inflammation and commonly caused the inflammation related diseases.[12-14] The intervention of anti-inflammatory medication toward the inflammation associated diseases could be one of the solution to overcome this entity.[15] Equally important, natural products derivate from plants, mostly flavonoids and phenolic constituents, have been used as classic therapy or medication to promote health and quality of life due to its therapeutic properties.[11]

Sambucus plant or elderberry is a group of shrub that widely found in almost of continents such as Europe, Asia, North Africa, and America.[16] The plant extracts of *Sambucus* contain bioactive-rich compounds especially flavonoids and phenolic.[17] Historically, *Sambucus* plants have been used as medical treatment against broad spectrum of diseasesin order to promoting health status. However, up to date, the study about the effect of

*Author for correspondence
Muhaimin Rifa'i, Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Indonesia.
Tel: 0341-575841; E-mail: rifa123@ub.ac.id

Table 1. Multiple *Sambucus* bioactive compounds and inhibitors used as ligand against the TNF-α or TRAIL.

No.	Bioactive Compound	Molecular Formula	CID	Remark
1	Protocatechuic acid	$C_7H_6O_4$	72	Compound
2	4-Hydroxybenzaldehyde	$C_7H_6O_2$	126	Compound
3	Benzoic acid	$C_7H_6O_2$	243	Compound
4	Hippuric acid	$C_9H_9NO_3$	464	Compound
5	3,4-Dihydroxyphenylacetic acid	$C_8H_8O_4$	547	Compound
6	Naringenin	$C_{15}H_{12}O_5$	932	Compound
7	Homovanillic acid	$C_9H_{10}O_4$	1738	Compound
8	3-Hydroxybenzoic acid	$C_7H_6O_3$	7420	Compound
9	4-Methylcatechol	$C_7H_8O_2$	9958	Compound
10	Phloroglucinolaldehyde	$C_7H_6O_4$	68099	Compound
11	Epicatechin	$C_{15}H_{14}O_6$	72276	Compound
12	Catechin	$C_{15}H_{14}O_6$	73160	Compound
13	Procyanidin B2	$C_{30}H_{26}O_{12}$	122738	Compound
14	Procyanidin B5	$C_{30}H_{26}O_{12}$	124017	Compound
15	Cyanidin	$C_{15}H_{11}O_6^+$	128861	Compound
16	Procyanidin C1	$C_{45}H_{38}O_{18}$	169853	Compound
17	Ferulic acid	$C_{10}H_{10}O_4$	445858	Compound
18	p-Coumaric acid	$C_9H_8O_3$	637542	Compound
19	Caffeic acid	$C_9H_8O_4$	689043	Compound
20	Quercetin	$C_{15}H_{10}O_7$	5280343	Compound
21	Isoquercitrin	$C_{21}H_{20}O_{12}$	5280804	Compound
22	Rutin	$C_{27}H_{30}O_{16}$	5280805	Compound
23	Kaempferol	$C_{15}H_{10}O_6$	5280863	Compound
24	Isorhamnetin	$C_{16}H_{12}O_7$	5281654	Compound
25	Kaempferol-3-rutinoside	$C_{27}H_{30}O_{15}$	5318767	Compound
26	Quercetin-3-rhamnoside	$C_{21}H_{20}O_{11}$	5353915	Compound
27	Isorhamnetin-3-rutinoside	$C_{28}H_{32}O_{16}$	17751019	Compound
28	Quercetin-3-glucoside	$C_{21}H_{19}O_{12}^-$	25203368	Compound
29	Pelargonidin-3-sambubioside	$C_{26}H_{29}O_{14}^+$	44256622	Compound
30	Cyanidin-3-sambubioside	$C_{26}H_{29}O_{15}^+$	74976920	Compound
31	Hyperoside	$C_{21}H_{20}O_{12}$	133568467	Compound
32	Thalidomide	$C_{13}H_{10}N_2O_4$	5426	Inhibitor
33	Lenalidomide	$C_{13}H_{13}N_3O_3$	216326	Inhibitor
34	Pomalidomide	$C_{13}H_{11}N_3O_4$	134780	Inhibitor

Sambucus in inflammation associated diseases is based on very limit data.[18] Therefore, this study aimed to predict the possibility of bioactive constituents of *Sambucus* plant as inflammatory inhibitor against inflammation associated diseases.

Experimental

Ligands retrieval and preparation – Accumulating evidence showed the *Sambucus* plants contain broad spectrum of bioactive compounds. In the present study, about 31 bioactive constituents (Table 1) from *Sambucus* plants were occupied against TNF-α and TRAIL protein model.[17-20] The therapeutic features of bioactive compounds were assessed by PASS online prediction.[21] Also, in this study, several inhibitors were used such as Thalidomide, Lenalidomide, and Pomalidomide as comparison control toward the bioactive compounds interaction with protein model (Table 1). All ligands 2D structure were retrieved from Pubchem and converted into sdf. format for next procedure.[22]

Homology modeling of protein – The TNF-α (P01375) and TRAIL (P50591) protein sequences were retrieved from UniProtKB.[12] Then, the 3D homology modeling of

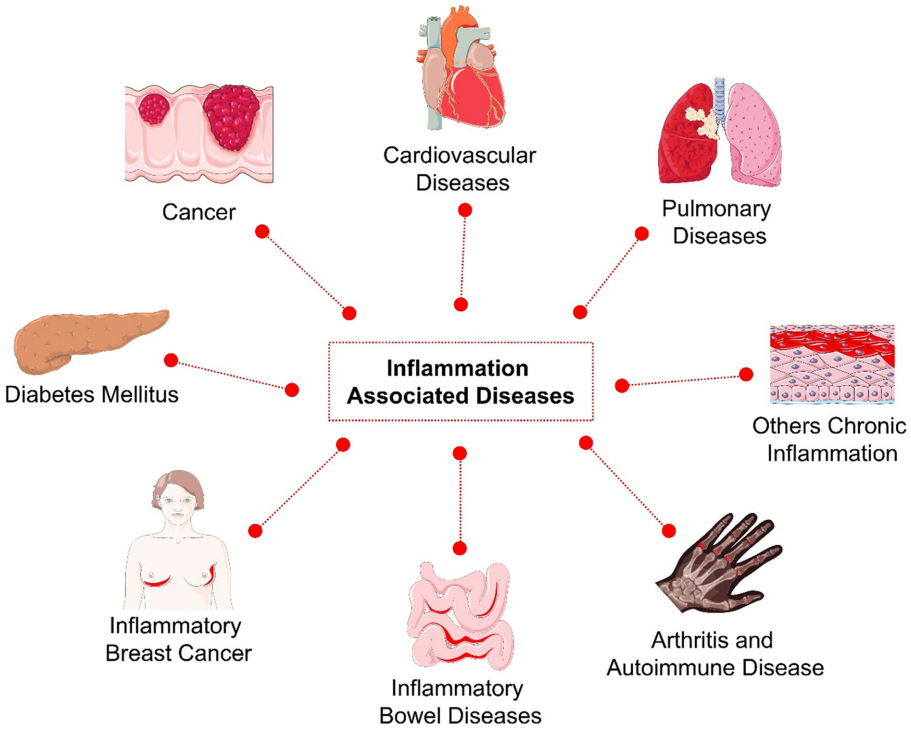

Fig. 1. Despite of their favorable function in innate immunity, the chronic inflammation also caused several types of diseases.

proteins have been done via SWISS-MODEL and converted into pdb. format for next procedure.[23]

Molecular docking and analysis – Docking materials were optimize as previous study.[24,25] After that, the docking simulation and prediction of ligand-protein were performed by using the AutoDock Vina in PyRx 0.8.[26] Lastly, the result visualization and analysis were done by Pymol and ADS Visualizer software.

Results and Discussion

Accumulating evidence showed that inflammation associated diseases directly caused by the failure of immune system to take control under acute inflammation, in turn the condition worsen and leads to the chronic status.[3,27] As metabolic disorder (Fig. 1), the chronic inflammation promotes multiple diseases such as cancer, cardiovascular diseases, pulmonary diseases, diabetes mellitus, inflammatory breast cancer, inflammatory bowel diseases, and arthritis and autoimmune diseases.[3,27-30] General pathophysiological condition revealed both acute and chronic inflammation induce tissues injury in most of organ system. Obviously, the molecular sign of this entity is following with the high production of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, and TNF-α.[3]

Recently, the most common treatment for these entities is inhibiting the production of pro-inflammatory cytokines by blocking the TNF-α or TRAIL with the inhibitory drugs. Even though this approach has been established for long time ago, but there is the classic treatment that might be more potential as anti-inflammation, called natural medicine.[31,32] As shown in Fig. 2, the proper way to suppress inflammation is by blocking the TNF-α or TRAIL as inflammation inducer with natural products, in this case the potency of *Sambucus* bioactive compounds. It has been reported that flavonoids and phenolic compounds exert their biological properties as anti-inflammation by blocking the activation of NF-κB and mitogen-activated protein kinase (MAPK).[11] Importantly, the TNF-α and TRAIL promote the pro-inflammatory cytokines and cell survival via the activation of NF-κB and MAPK. Therefore, by blocking the TNF-α and TRAIL can prevent the worst condition from the inflammation.[31,32]

Numerous studies demonstrated the elderberry and elderflower contain several bioactive compounds such as flavonols, proanthocyanidins, anthocyanins, and other phenolic acids and metabolites as shown in Table 1. It has reported that the bioactive compounds have wide range of biological activities like anti-inflammatory, antioxidant, and antidiabetes.[17-19] Interestingly, based on the molecular docking prediction there are three selected bioactive compounds regarding their greatest potency to interact

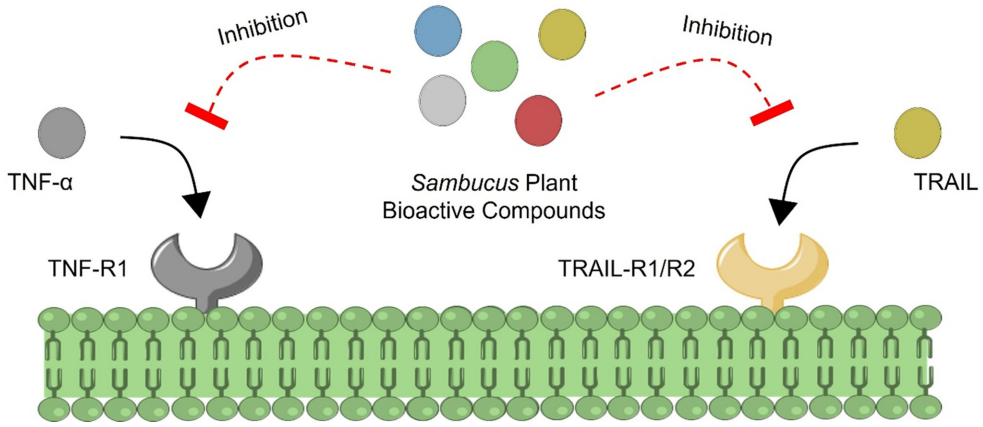

Fig. 2. Schematic illustration shows the hypothesis about the inhibition of *Sambucus* bioactive compounds to TNF-α or TRAIL may suppress the inflammation rate.

Table 2. Top three bioactive compounds with the greatest binding affinity value compared with the inhibitors

No.	Protein	Ligand	Binding Affinity	Amino Acid Residues
1	TNF-α	Caffeic acid	-6.4 kcal/mol	VAL93, ALA94, PRO96, ARG108, ALA109, ASN110, VAL167, ASN168, LEU169, PHE200, PHE220, GLU222, SER223, GLY224, GLN225, VAL226
		Protocatechuic acid	-6.3 kcal/mol	GLN137, LYS174, PRO193, ILE194, TYR195, LEU196, ALA172
		3-Hydroxy-benzoic acid	-6.1 kcal/mol	GLN137, LYS174, PRO193, ILE194, TYR195, LEU196
		Thalidomide (Inhibitor)	1.1 kcal/mol	GLN137, LYS174, PRO193, ILE194, TYR195, LEU196, ALA172, GLU192
2	TRAIL	Homovanillic acid	-6.6 kcal/mol	ARG227, SER241, ILE242, TYR243, GLN187, SER225, GLN244
		3,4-Dihydroxy-phenylacetic acid	-6.5 kcal/mol	ARG227, SER241, ILE242, TYR243, TYR240
		Protocatechuic acid	-6.3 kcal/mol	ARG227, SER241, ILE242, TYR243, SER225, GLN187, TYR240, GLN244
		Lenalidomide (Inhibitor)	-4.0 kcal/mol	ARG227, SER241, ILE242, TYR243, GLN187, SER225, ALA226, ARG243, TYR240, GLN244

with TNF-α such as caffeic acid (-6.4 kcal/mol), protocatechuic acid (-6.3 kcal/mol), and 3-hydroxy-benzoic acid (-6.1 kcal/mol). These compounds have better binding free energy compared to the control as the thalidomide just count about 1.1 kcal/mol for binding free energy to the TNF-α (Table 2). Caffeic acid (3,4-dihydroxy-cinnamic acid) is natural compound that abundantly provided in numerous plants such as potato, carrot, apple, and berries.[33,34] It has been widely demonstrated that caffeic acid exerts its biological activities as anti-diabetic, anti-oxidant, and anti-inflammation.[35-39] Moreover, based on several studies, the caffeic acid isolated from *Rhodiaola sacra* and propolis has been reported to act as inflammation suppressor in lipopolysaccharide-treated inflammatory mouse model.[40,41] The molecular mechanism of action how the caffeic acid plays as anti-inflammatory agent through inhibiting some of enzyme activities related to inflammation such as xanthine oxidase and cyclooxygenase. Interestingly, the caffeic acid also inhibit the activation of NF-κB to reduce the production of pro-inflammatory cytokines.[36,41] Additionally, the molecular docking prediction also showed the top three greatest binding free energy among the TRAIL with the ligands such as homovanillic acid (-6.6 kcal/mol), 3,4-dihydroxy-phenylacetic acid (-6.5 kcal/mol), and protocatechuic acid (-6.3 kcal/mol). Importantly, these respective compounds have better potency to interact with the TRAIL compared to lenalidomide (-4.0 kcal/mol) as the control (Table 2). Homovanillic acid (3'-methoxy-4'-hydroxyphenylacetic acid) is largely known as the final product of dopamine degradation through dopamine oxidative metabolism.[43-45] Homovanillic acid has been used as health-promoting therapy agent

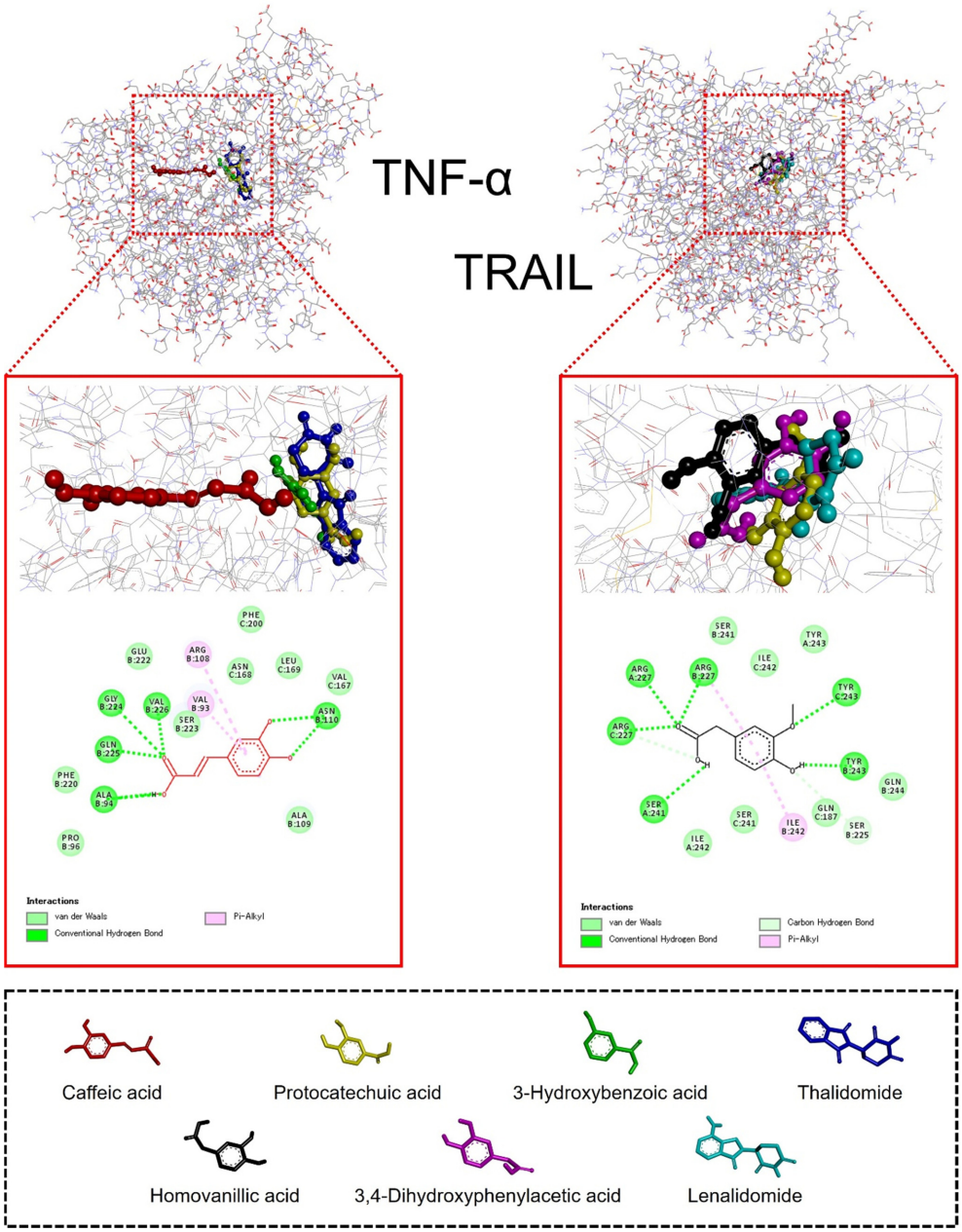

Fig. 3. Molecular docking of protein – ligands. The amino acid residues show the specific interaction to ligand. Left panel – TNF-α interacts with caffeic acid, protocatechuic acid, 3-hydroxybenzoic acid, or thalidomide. Right panel – TRAIL interacts with homovanillic acid, 3,4-dihydroxyphenylacetic acid, protocatechuic acid, or lenalidomide.

because it possesses the antioxidant and antiradical activity.[46]

On the other hand, the docking prediction also showed numerous of amino acids residues that interact with the ligands (Fig. 3). Surprisingly, on the TNF-α – ligands interaction showed the similar amino acid residues such as GLN137, LYS174, PRO193, ILE194, TYR195, and LEU196 that found in protocatechuic acid, 3-hydroxy-benzoic acid, and thalidomide interaction but not in caffeic acid. In the same way, on the TRAIL – ligands interaction also showed the similar amino acid residues such as ARG227, SER241, ILE242, and TYR243 that found in homovanillic acid, 3,4-dihydroxy-phenylacetic acid, protocatechuic acid, and lenalidomide interaction (Table 2). These results suggest that the accuracy of ligands interaction on the both protein models seemly are in the similar interaction coordinate. To greater extent, to understand more about the protein-ligands interaction features, this study explored the additional characters such

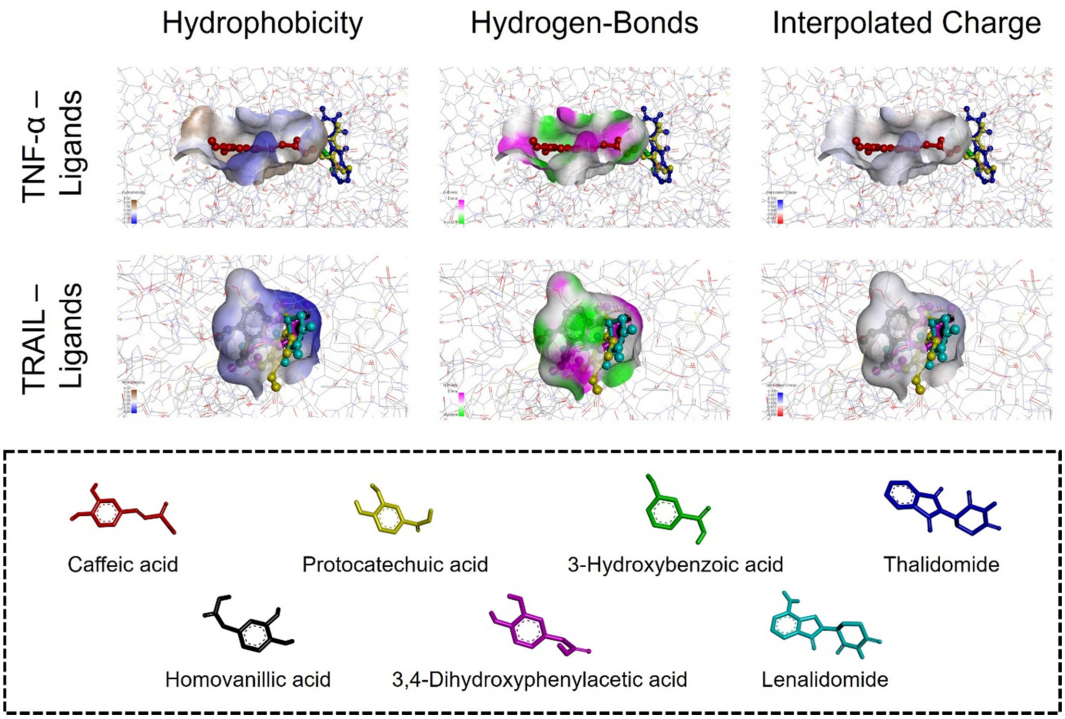

Fig. 4. Molecular interaction characters such as hydrophobicity, hydrogen-bonds, and interpolated charge on TNF-α or TRAIL interaction with the ligand. Upper panel – TNF-α interacts with caffeic acid, protocatechuic acid, 3-hydroxybenzoic acid, or thalidomide. Bottom panel – TRAIL interacts with homovanillic acid, 3,4-dihydroxyphenylacetic acid, protocatechuic acid, or lenalidomide.

as hydrophobicity, hydrogen-bonds, and interpolated charge (Fig. 4). On the protein-ligand binding, the hydrogen bonding and hydrophobicity are playing pivotal role in maintenance the protein structure and stabilizing the interaction. Moreover, the optimizing of hydrophobicity and hydrogen bonding promotes the binding affinity of the protein-ligand interaction which in turn this phenomenon can be considered as sign of good efficacy of drug.[46] Additionally, the protein surface isoelectric also considered as one of the crucial part that determine the interaction stability.[47]

In conclusion, the results of the study showed that caffeic acid and homovanillic acid have the greatest binding against the TNF-α and TRAIL respectively. This evidence suggests that caffeic acid and homovanillic acid may potent as anti-inflammatory agents against the inflammation associated diseases. Finally, this study need further examination and evaluation to validate the potency of *Sambucus* bioactive compounds.

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