

Evaluation of *In Silico* and *In Vitro* Inflammatory and Biofilm Targets Inhibition by the Polyphenols of *Prunus persica L. Spp*; Functional Food Based Approach for the Illnesses Associated with Inflammatory and Microbial Pathways

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ABSTRACT

Aims and objectives: Considering the increasing resistance of bacteria to antibiotics and the presence of antibacterial agents in plants being served as functional food choice for many ailments. Chronic diseases become the leading cause of more than 50% of deaths around the world. The real reason is inflammation linked to the microbial association as biofilm trend behind all chronic diseases like congestive heart failure, cognitive disorders, diabetes and associated comorbidities, hypertension. Bioactive compounds in functional foods are responsible for all these health benefits present in them. Research has suggested that fruits of *Prunus persica L.* rich in polyphenolic constituents as major bioactive compounds that possess remarkable antibacterial properties. The aim of this study was to evaluate the anti-biofilm and anti-inflammatory potential of the polyphenolic constituents of the fruits of *Prunus persica L.*

Methodology: During this project, both *in vitro* and *in silico* models were adopted to investigate the objectives of the study. Several fractions of the peel of *Prunus persica* were subjected to initial antimicrobial and anti-biofilm screening. Based on structural diversity, selected pure compounds were screened for putative binding sites and molecular docking studies followed by enzymatic analysis of 15 LOX inhibition and anti-biofilm potential.

Results and discussion: The negative binding energies and close proximity to residues in the binding pocket of selected targets including human α -soybean LOX (PDB ID 1IK3) and LasR (2UV0) were recorded, which indicated high affinity and tight binding capacity of gallic acid and Ferulic acid towards the active sites of LasR 2UV0 and 15-lipoxygenase. P-coumaric acid exhibited the highest inhibition of 15-lipoxygenase *in vitro* (70%, at 0.033 mM final concentration) and that is accompanied by ferulic acid (65%), whereas in the biofilm inhibition assay, gallic acid was most active (IC₅₀ 0.05 mM), followed by Chlorogenic acid (IC₅₀ 0.07 mM), It was therefore concluded that gallic acid and Chlorogenic acid had the highest biofilm inhibitory activity, whereas ferulic acid and p-Coumaric acid were potent 15-lipoxygenase inhibitors with potentially anti-inflammatory properties.

Conclusion: By considering the results obtained and increasing resistance of bacteria to chemical antibiotics, it is suggested that several bacterial infections and associated inflammatory conditions may be treated using the above functional food based approach by employing the polyphenolic constituents of the *Prunus persica L.*

Keywords: Biofilm; 15 Lox; Functional foods; Transcriptional regulators; Molecular docking; HYDE assessment

INTRODUCTION

Functional foods are foods or dietary components that have the potential to provide health benefits beyond basic nutrition.

A food can be made functional by using any technological or biotechnological means to increase the concentration of, add,

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remove, or modify a specific component, as well as improve its bioavailability, provided that component has been shown to have functional effect, introducing the conception of probiotics and prebiotics, which may affect microbial configuration and activities [1].

Prunus persica L. is a member of the *Rosaceae* family and is one of the most popular stone fruits for direct consumption as well as an interesting material for the food industry. *P. persica* (*Rosaceae*) is the second most widely cultivated fruit tree [2]. Because of its bioactive constituents (phenols and carotenoids), peach fruit is well-known for its nutritional value and therapeutic properties [3]. As a result, significant efforts have been directed toward estimating the bioactivity and functionality present in various peach varieties in order to evaluate the potential of peach fruits. Several studies examined the bioactive constituents of *P. persica* extracted with various solvents. Methanol was the most commonly used of them all [4].

Phenolic compounds are a diverse and large class of compounds. The nature of those compounds varies from organ to organ within each plant species but remains constant. It is well known that traditional fruits and vegetables have numerous health benefits [5]. The beneficial effects of these natural products are attributed to their bioactive compounds, primarily phenolic compounds and glycosides [6-8]. It is well understood that phenolic compounds have antioxidant properties and help to prevent the oxidation of low density lipoprotein cholesterol (LDL-C) [9]. Fruits' health-promoting properties are due to the presence of some secondary metabolites, such as phenols, which have received a lot of attention due to their disease-fighting potential. Furthermore Microbial pathogenesis is thought to be the link between disease onset and aging-related inflammation [10].

Biofilms are accumulation of microorganisms attached to the surface and embedded in a polymeric substance extracellular, with cell masses ranging from 10⁸ to 10¹¹ cells g⁻¹ [11,12]. Biofilms are the most common type of successful and distinct life on the planet. Biofilms are actually adaptations of various systems. Biofilm producing microbes can infiltrate higher organisms, including humans and may be linked to obstinate infections in humans, plants, and animals [13,14]. One of the most dangerous implications involved in many localised type infections of chronic nature that offer resistance to conventional antibiotics is the microbial biofilm [15]. Microorganisms in biofilms adapt to available conventional therapeutic options by modifying molecular or metabolic pathways, resulting in resistance [16]. With greater understanding of the ingredients contained in stone fruit kernels and their health-promoting potential, there is growing interest in their use for human consumption, particularly to enrich man's diet with compounds beneficial in the prevention of chronic inflammation and a variety of diseases [17-19].

According to a review of the literature, Polyphenolic compounds isolated from *Prunus persica L.* plants have a wide range of activities, including anti-leishmanial, anti-inflammatory, cytotoxic, anticancer, antibacterial, and antiviral properties [20,21]. It has been suggested by several investigations [22]. Immunological changes (including chemokine and cytokine levels) caused by inflammation may increase the pathogenicity of microbial infections, and a cross-dependent relationship has been discovered. Therefore, we aimed

to use *in vitro* and *in silico* techniques to investigate the antibiofilm and anti-inflammatory activities (15 LOX inhibition) of the Polyphenolic compounds from the peel of *Prunus persica L.*

MATERIALS AND METHODS

Bacterial strains, growth media and chemicals

The commercial strains used during investigation included *Staphylococcus aureus* (ATCC 33862) and *Pseudomonas aeruginosa* (ATCC 15442). The bacterial growth media used included, Tryptic Soya Broth (TSB), nutrient agar (Hi Media, India) Luria-Bertani Broth (LB) (Oxoid). The standard compounds were purchased commercially -the Polyphenolic compounds i.e., Gallic acid (A), Protocatechuic acid (B), Chlorogenic acid (C), p-Coumaric acid (D) and Ferulic acid (E) [23]. were purchased commercially, including Gallic acid (Fluka Honeywell, Seelze, Germany), quercetin (Sigma Aldrich, St. Louis, MO, USA), Protocatechuic acid (Fluka Honeywell, Seelze, Germany), ciprofloxacin (Sigma Aldrich, St. Louis, MO, USA) ferulic acid (Sigma Aldrich, Steinheim, Germany), chlorogenic acid (Sigma Aldrich, Steinheim, Germany), p-coumaric acid (Fluka Honeywell, Seelze, Germany). All the chemicals purchased were of analytical grade.

The plant material: Plant materials were purchased from the local market of Islamabad Pakistan and were authenticated in the department of Botany Quaid e Azam University Islamabad. The Peel extract was prepared by cold maceration (90% methanol) for 10 days (repeated three times) and further liquid-liquid fractionation was accomplished using a rotary evaporator (40°C). The dried plant material was stored at -4°C until further usage. The schematic fractionation scheme is attached with supplementary material.

Phytochemical analysis: The phytochemical screening for different chemical classes was performed according to the published reference.

Thin layer chromatography: The TLC was accomplished by using analytical TLC F254 plates (20 × 20 cm) (Merck) for normal phase. Various solvents systems were tried for a complete separation of bands. For observation, UV lamp (360 nm) and spraying with reagent p-anisaldehyde, reagent was employed.

Chromatographic analysis/HPLC profiling: A detailed HPLC analysis of total extract was performed using Agilent® 1200 series system (HPLC-DAD, Agilent Technologies and Santa Clara, CA, USA). The samples (10 µL) were injected at a flow rate of 1 mL/min with acetonitrile: water (0.1% formic acid) gradient (5% Acetonitrile to 100% in 40 min). Samples were prepared in a concentration range from 1 to 10 mg/mL in methanol. A Phenomenex Luna C18 column (silica-based, 250 × 4.6 mm, 5 µm) (Phenomenex, Torrance, CA, USA) was used.

Molecular docking

Ligand and protein structure preparation: For docking studies, the X-ray crystallographic structures of transcriptional regulators LasR (2UV0), (Yu et al.) and soybean LOX (PDB ID 1IK3) were extracted from the RCSB Protein Data Bank [24,25]. The 3D structures of the test compounds were prepared by MOE builder tool (MOE 2014) and energy minimization was done at MMFF94x force field (Labute). Afterwards the energy minimization and protonation of downloaded proteins was carried out by MOE (2014). A total

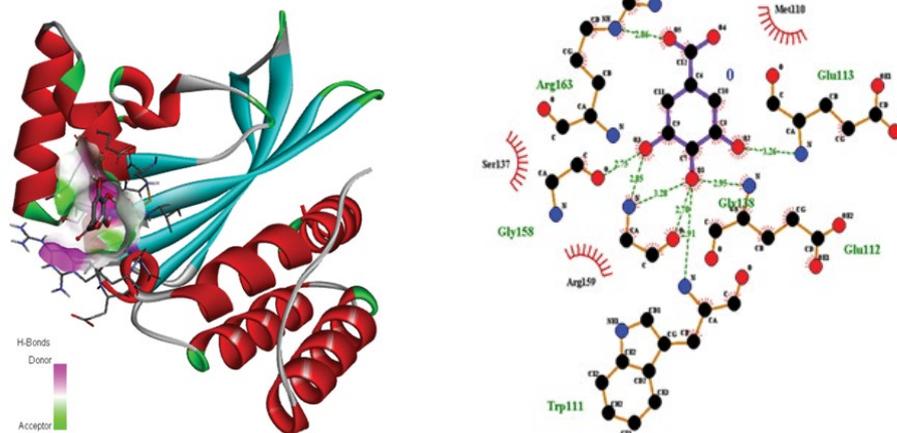


Figure 2: 3D interaction and H, non-H Bonding interactions of Gallic acid inside binding sites of transcriptional regulator 2UV₀ with the pose rank 1.

Note:  : Ligand bond;  : Non-ligand bond;  : Hydrogen bond and its length;  : Non-ligand residues involved in hydrophobic contact(s);  : Corresponding atoms involved in hydrophobic contact(s).

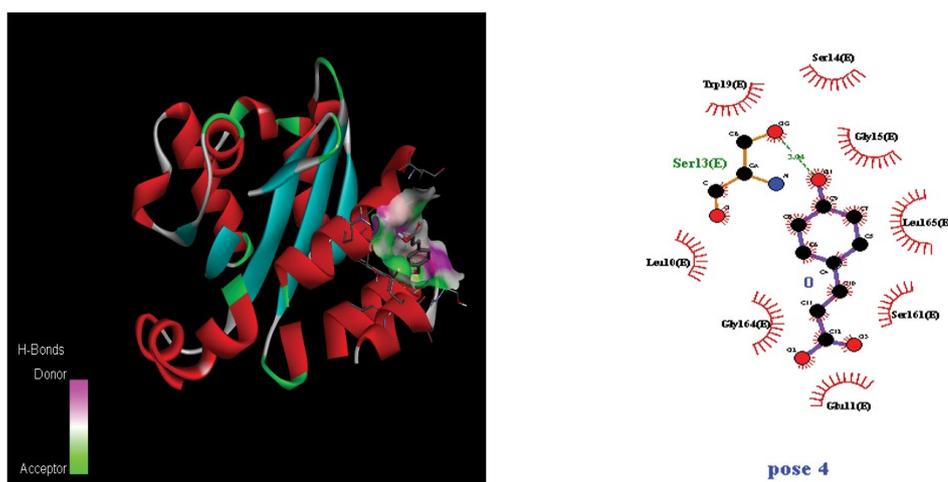


Figure 3: 3D interaction and H, non-H Bonding interactions of P-Coumaric acid inside binding sites of transcriptional regulator 2UV₀ with the pose rank 4.

Note:  : Ligand bond;  : Non-ligand bond;  : Hydrogen bond and its length;  : Non-ligand residues involved in hydrophobic contact(s);  : Corresponding atoms involved in hydrophobic contact(s).

earlier reports. All the docked molecules occupied well the binding pocket site and presented several important interactions. The 3D and 2D interaction diagrams of all the compounds are given in Figures 4-7.

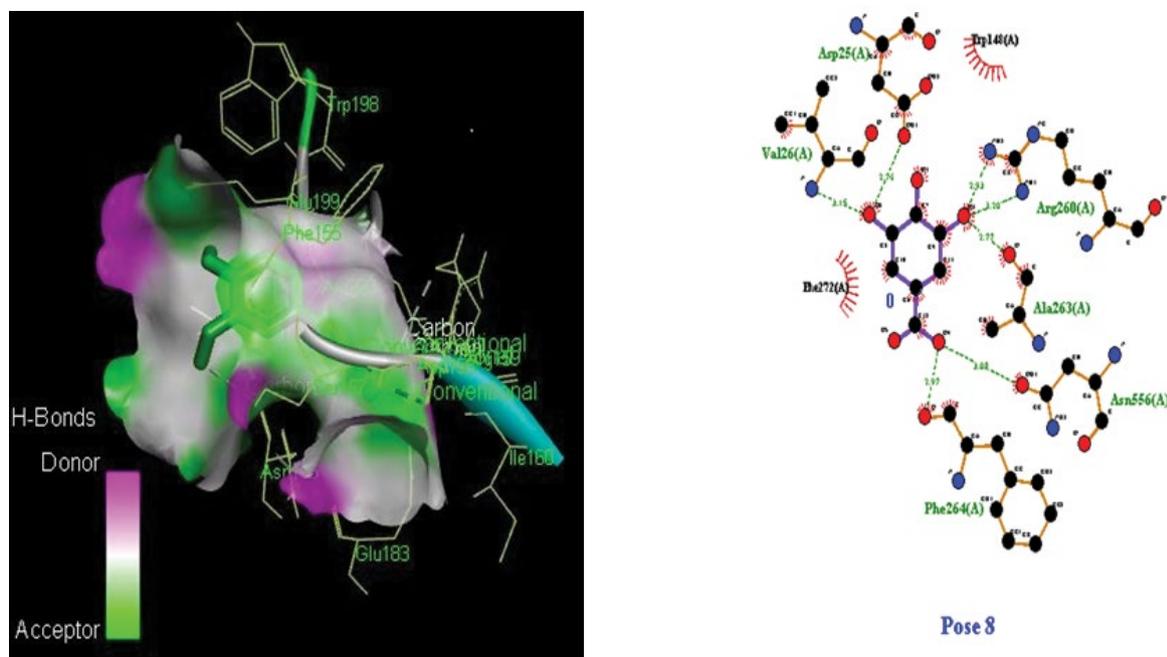
15-LOX docking

Molecular docking studies of test compounds was carried out for the possible inhibition of soybean 15-LOX PDB 1IK3 in Table 1. Along with the FlexX score of the top ranking pose, HYDE assessment provided the binding free energies of all the test compounds within the active pockets of receptors. Molecular docking studies of all test compounds were carried out inside the soybean 15-LOX PDB

1IK3. The results are depicted in Figures 4-7 and supplementary Figures 1-7. Among all compounds, the most notable interaction was seen with regard to compound 1 in Figure 4 that was inside the binding pocket of 1IK3 encompassing hydrogen bonding with residues Phe 264, Asn556, Ala263, Arg260, Asp25, Val26, the common hydrogen bonding interaction with residue Arg 200 is shown by the ligand of 1IK3, Chlorogenic acid and p-Coumaric acid. The putative interactive mode of compound 1 is shown in Figure 4. To the left side, the 3D interactions are shown, whereas on the right side, a cartoon view of the docked compound inside 1IK3 is displayed. Similarly, compound 3 and 5 appeared to be potent inhibitor of 15 LOX. It was found to bind inside the active site of 1IK3 with a binding free energy of -9.2 and -5.7 kJ mol⁻¹ with the best

Table 1: Docking score, H and non H-bonding interactions of tested compounds.

Compound	Binding free energy ΔG (kJ mol ⁻¹)	Pose rank	No of H bonds	H Bond interaction residues	Other interaction residues
Gallic acid	-5.8	1	5	Glu112, Arg163, Gly158, Gly138, Trp111	Met110, Arg159, Ser137, Ile139
Protocatechuic acid	-6	8	0	-	His 63, Trp 60, Glu 104, Pro 57, Lys 34, Gly 109 Ala 107, Ala 108
Chlorogenic acid	-6.1	1	3	Pro 149, Phe 7, Gly 6	Ile22, Tyr 157, Trp 152, Leu 33, Trp 153
p-Coumaric acid	-5.3	8	1	Ser 13	Glu11, Ser161, Leu 165, Gly15, Ser 14,Trp19, Ser13, Leu 10,
Ferulic acid	-5.6	6	2	Glu 11, Gly 15	Trp 19, Gly 164, Ser161, Leu165, Ser14, Ser13, Leu10,
Quercetin	-8.8	5	7	Tyr46, Asp65, Arg61,Trp60 Ser129, Thr75, Thr115	Trp88, Ala127, Leu36, Val76, Ile52, Gly38, Ala50, Tyr64, Leu110, Tyr56, Asp73
1IK3					
Gallic acid	-5.6	8	6	Phe 264, Asn556, Ala263, Arg 260, Asp25, Val 26	Trp 148, Phe 272
Protocatechuic acid	-5.3	9	5	Asp 428, Asp 382, Arg 386, Cys 379, Lys 381	Arg 378, Pro 385, Leu 380, Leu 426
Chlorogenic acid	-9.2	1	6	Asn 534,Tyr 202, Arg 200, Tyr 544, Asp 787, Asn 788	Asp 261, Ser 147, Trp 791, Phe1 61, Val 539, Pro 789
p-Coumaric acid	-6.1	1	4	Arg 159, Arg 200 , Asn 186, Ser 157	Ile201, Glu 199, Phe1 155
Ferulic acid	-5.7	5	5	Ala 705, Ser 706, Ile 772, Ser 774, Arg 775	Leu 708, Thr 522, Ile 855, Ala 710,Ser 856, Ser 854, Pro 852

**Figure 4:** 3D interaction and H, non-H Bonding interactions of Gallic acid inside binding sites of transcriptional regulator 1Ik3 with the pose rank 8.

Note: : Ligand bond; : Non-ligand bond; : Hydrogen bond and its length; : Non-ligand residues involved in hydrophobic contact(s); : Corresponding atoms involved in hydrophobic contact(s)

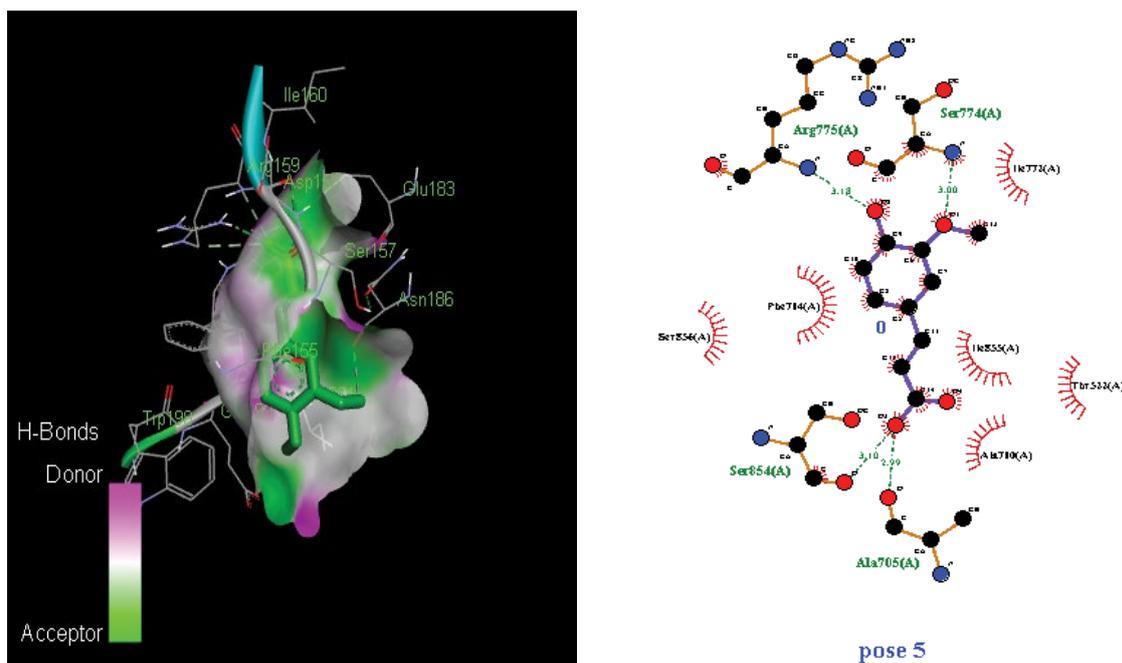


Figure 5: 3D interaction and H, non-H Bonding interactions of Ferulic acid inside binding sites of transcriptional regulator 11k3 with the pose rank 5.

Note: : Ligand bond; : Non-ligand bond; : Hydrogen bond and its length; : Non-ligand residues involved in hydrophobic contact(s); : Corresponding atoms involved in hydrophobic contact(s).

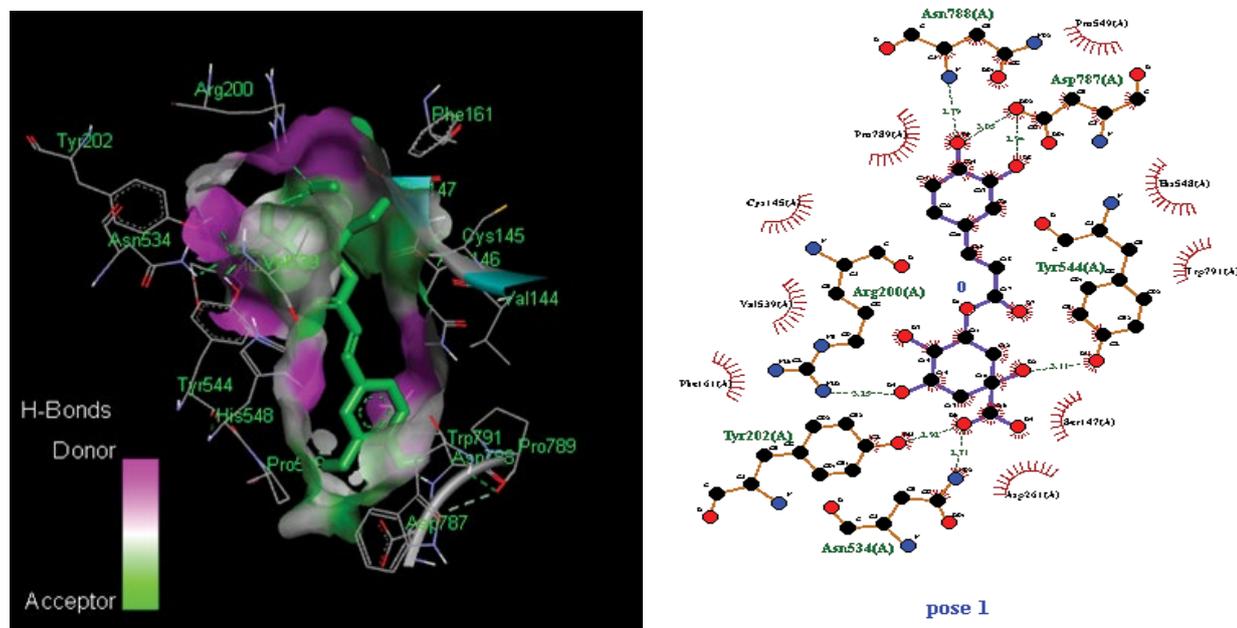
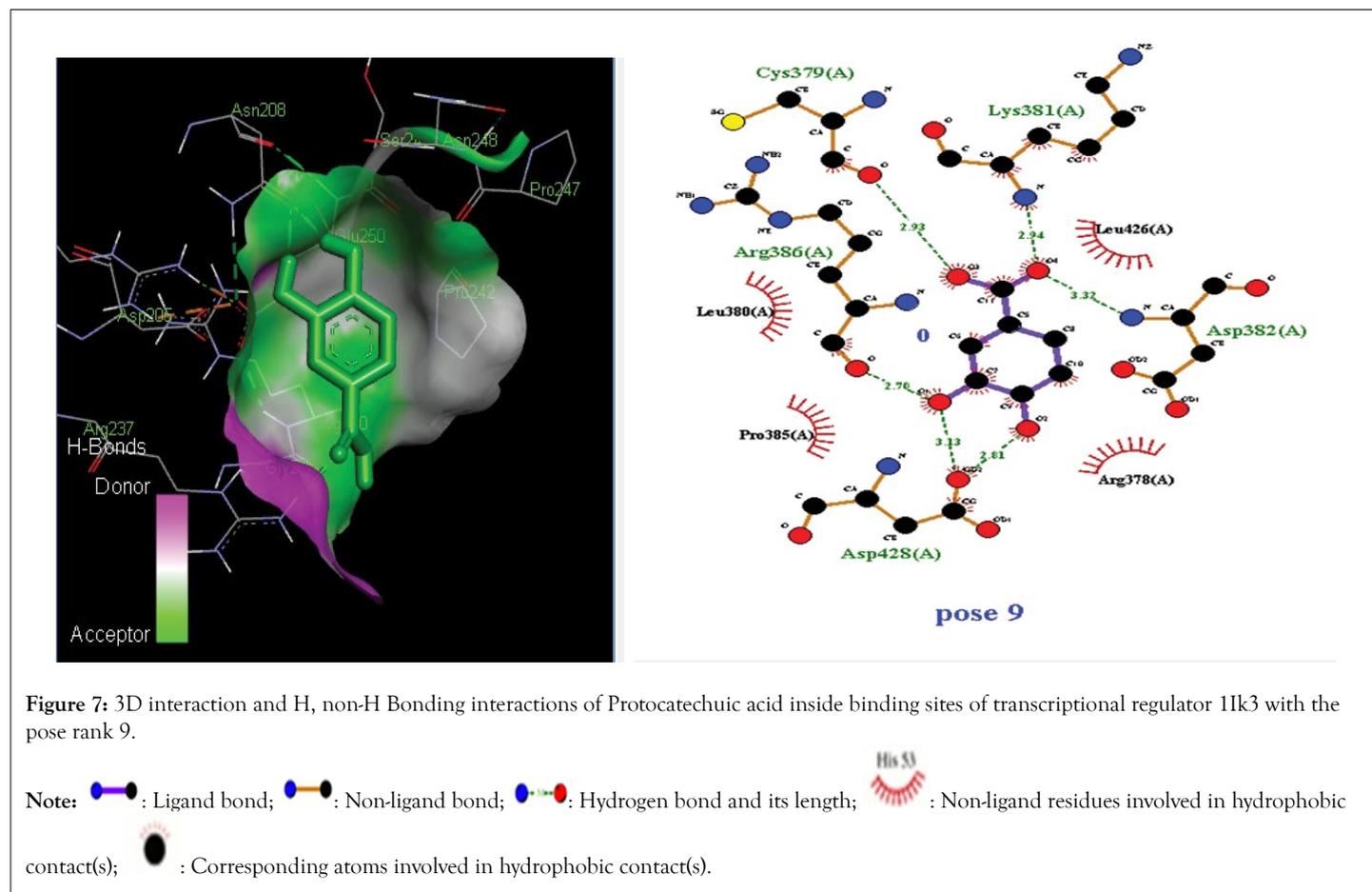


Figure 6: 3D interaction and H, non-H Bonding interactions of chlorogenic acid inside binding sites of transcriptional regulator 11k3 with the pose rank 1.

Note: : Ligand bond; : Non-ligand bond; : Hydrogen bond and its length; : Non-ligand residues involved in hydrophobic contact(s); : Corresponding atoms involved in hydrophobic contact(s).



pose rank of 1 and 5 respectively. On the other hand, compound 4 gave hydrogen bonding interactions with Arg 159, Arg 200, Asn 186, Ser 157. Based on interactions, important residues involved in the formation of hydrogen bonds and π - π interactions for all other compounds were Phe 264, Asn556, Ala263, Arg 260, Asp25, Val 26, Asp 428, Asp 382, Arg, Arg 159, Arg 200, Asn 186, Ser 157. The facts describe the interactions of secluded compounds inside the soybean 15-LOX 1IK3 (Figure 8).

HYDE assessment of compounds against all the targets: The HYDE affinity assessment was done for the first 30 top ranked docking conformations within the active sites of 1IK3 and 2UV0 and it helped in the selection of the correct binding mode. The binding free energy ΔG , FlexX docking score and the most favorable poses for all the compounds are given in Table 1. The compounds bind to the receptor with a very high binding affinity and give favorable contributions.

In vitro analysis: The isolated fractions of the extracts of peel of *Prunus persica L* were initially analyzed for determination of MIC and MBC against biofilm producer strain *Pseudomonas aeruginosa* (ATCC 15442). Among all fractions, methanol extract exhibited significant activity (MIC 0.018 mg/mL, MBC 0.018 mg/mL) and followed by Aqueous and chloroform fractions (MIC 0.29 mg/mL, MBC 0.29 mg/mL) Table 2, whereas other fractions produced no significant inhibition of the strain (MIC>3 mg/mL). The fractions were also screened for *Staphylococcus aureus* (ATCC 33862) as well since it's the most common pathogenic bacteria involved in many diseases and inflammatory conditions and the results were found to be significant. Among all fractions, methanolic fraction followed

by chloroform and Aqueous were able to show remarkable biofilm as well as 15 LOX inhibition (Tables 3 and 4). Pure compounds were further tested for the antibiofilm potential against the biofilm producing strain *P. aeruginosa* (ATCC 15442). Amongst all analyzed compounds, compound A displayed highest biofilm inhibition followed by 3 and 5 with the IC₅₀ value of 0.05, 0.07 and 0.28 respectively (Table 5).

On the other hand, in case of 15-LOX inhibition, compound D and E (0.033 mM final concentration) presented excellent inhibition (70% and 65%) whereas low inhibition was recorded for the other compounds in Table 5. The structural features may be involved in 15-LOX inhibition (Tables 6-8).

ADMET analysis: The ADMET properties of all compounds are shown in Table 2. The feature TPSA is related to the absorption properties of compounds, whereas Consensus Log Po/w is indicator for lipophilicity. It was evident that TPSA topological polar surface area was less than 100 that indicates good oral absorption or membrane permeability [31-35]. Likewise the compounds presented High to moderate lipophilicity [36,37]. The physicochemical and toxicity risk assessments were carried out using SWISS ADME explorer. The results are presented such as solubility, Topological Surface Area (TPSA), bioavailability, drug likeness and physicochemical characteristics. All compounds showed good solubility between -1.64 and -2.11. All five compounds were predicted to have strong drug likeness properties except compound C which showed only one violation of Lipinski rule of five. The toxicity risk assessment shows that compounds pose no risk as almost all were predicted to be occupying toxicity

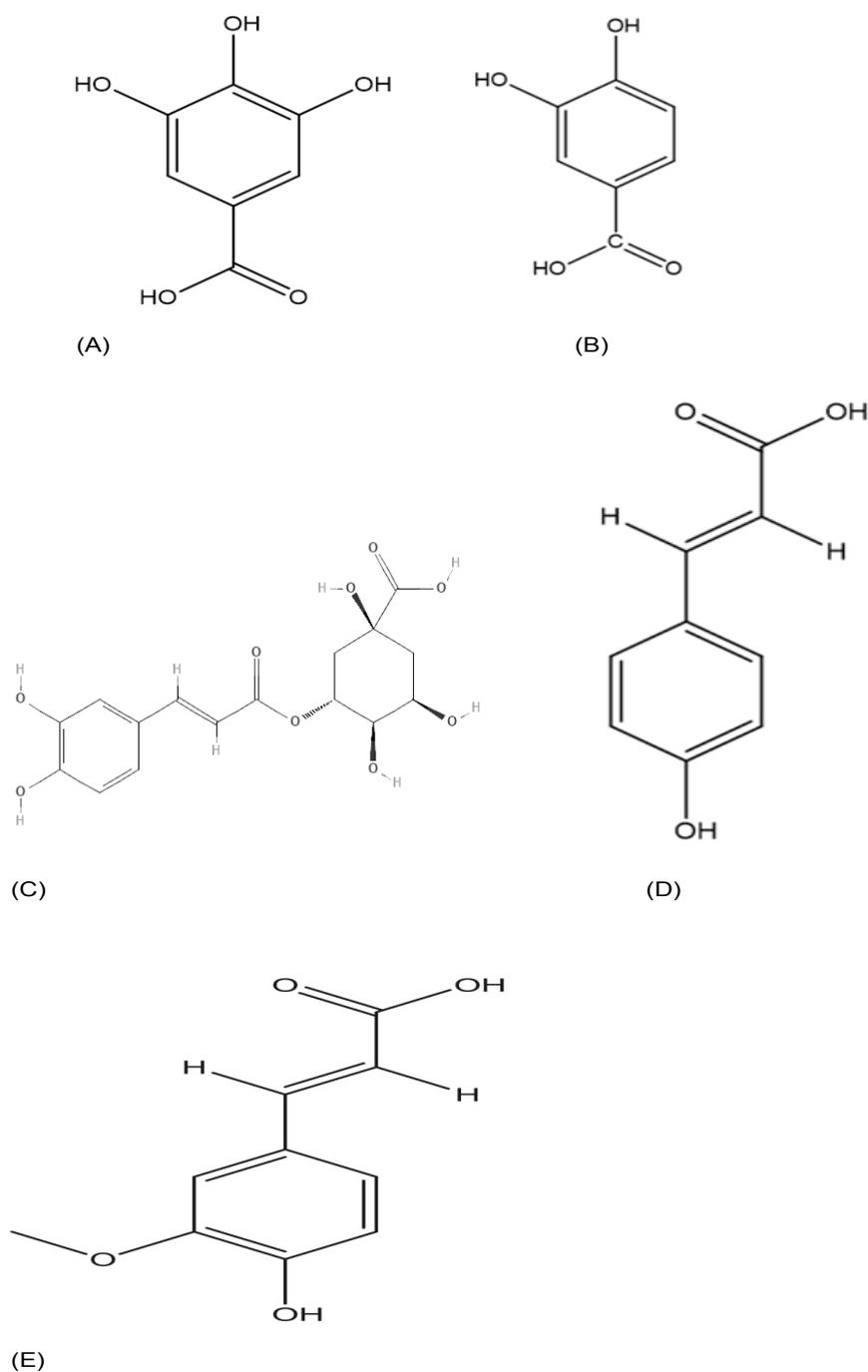


Figure 8: The structures of standard commercial compounds used, A: Gallic Acid; B: Procatechuic acid; C: Chlorogenic acid; D: P-coumaric acid; E: Ferulic acid.

Table 2: Antimicrobial properties of different fractions of extracts of peel of *Prunus persica L.*

Extracts	<i>Staphylococcus</i>		<i>Pseudomonas aeruginosa</i>	
	MIC (mg/dl)	MBC (mg/dl)	MIC (mg/dl)	MBC (mg/dl)
MeOH fract.	0.03	0.03	0.18	0.18
Ethyl acetate	3.6	≥ 3.6	2.56	≥ 2.56
Chloroform	0.17	≥ 0.17	2.6	2.6
N-Hexane	4.2	≥ 4.2	3.1	≥ 3.1
Aqueous	0.48	≥ 0.48	0.29	0.29
Standard ^a	10	10	10	10

Note: a= Ciprofloxacin 10 µg /ml

Table 3: Antibiofilm properties of different fractions of extracts of peel of *Prunus persica* L.

Extract part	Biofilm inhibition (IC ₅₀ mM)
MeOH fraction	0.08
Ethyl acetate	Not active
Chloroform	0.09
N-hexane	Not active
Aqueous	0.27
Standard ^a	0.0231

Note: a=Quercetin (mM)

Table 4: Anti-inflammatory (15 LOx inhibition) by different fractions of the extracts.

Extract part	15 LOX (%inhibition)
MeOH extract	60
Ethyl acetate	Not active
Chloroform	36
N-hexane	28
Aqueous	65
Standard	66 ^a

Note: a=Quercetin (mM)

Table 5: Biofilm inhibition and 15 LOX inhibition exhibited by pure compounds.

Compound	Biofilm inhibition (IC ₅₀ mg/ml)	15-LOX (% inhibition)
1	0.05	48
2	Not active	28
3	0.07	58
4	Not active	70
5	0.28	65
Standard	0.0221 ^a	182 ^b

Note: a=Ciprofloxacin µg/ml; b=Quercetin (mM), *(final concentration 0.033 mM final)

Table 6: ADMET analysis of the tested compounds.

Properties	Compounds				
	1	2	3	4	5
TPSA	97.99	77.6	164.75	57.53	66.76
Consensus Log Po/w	0.21	0.66	-0.38	1.26	1.36
Absorption					
Log S (ESOL) (water solubility)	-1.64	-1.86	-1.62	-2.02	-2.11
Pharmacokinetics					
GI absorption	High	High	Low	High	High
BBB permanent	No	No	No	Yes	Yes
Pgp substrate	No	No	No	No	No
CYP1A2 inhibitor	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No
CYP3A4 inhibitor	Yes	Yes	No	No	No
Log Kp (skin permeation)	-6.84	-6.42	-8.76	-6.26	-6.41
Drug likeness					
Lipinski	0	0	1	0	0
Bioavailability score	0.56	0.56	0.11	0.85	0.85
Toxicity					
Predicted LD50	2000	2000	5000	5000	1772
Predicted toxicity class	4	4	5	5	4

Table 7: Quantitative phytochemical analysis of extracts of peel of *Prunus persica* L.

Extract part	Flavonoids	Terpenoids/Steroids	Alkaloids	Tannins	Saponins
MeOH fract.	+++	++	~	~	~
Ethyl acetate	+++	++	~	~	~
Chloroform	++	++	~	~	~
N-Hexane	+	~	~	~	~
Aqueous	++	++	~	+	~

Table 8: MIC and MBC values of pure compounds against *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Compound	<i>Staphylococcus</i>		<i>Pseudomonas aeruginosa</i>	
	MIC (mg/dl)	MBC (mg/dl)	MIC (mg/dl)	MBC (mg/dl)
1	0.28	0.28	0.25	0.25
2	4.2	≥ 4.2	3.56	≥ 3.56
3	0.076	0.012	0.068	0.068
4	5.2	≥ 5.2	3.1	≥ 3.1
5	1.87	≥ 1.87	0.099	0.099
Ciprofloxacin ^a	8	8	8	8

Note: a=μ g/ml

class five or nearest to five. Relatively all the compounds were able to possess good GIT absorption with no inhibition of the p-gp substrate. Among all, compounds D and E were predicted to cross the blood brain barrier. The detailed analysis of ADMET is shown in Table 6.

DISCUSSION

The binding affinities of compounds A, C and E are in correlation with the experimental data as these compounds exhibited good inhibitory activity against biofilm and 15 LOX. The binding free energies and FlexX score showed that the compounds bind well into the active pocket with the good binding affinities and revealed favourable interactions. Interestingly there was very significant 15 LOX inhibition recorded for compound D (70%), unlike biofilm target, that are accordance with the best putative binding site and hydrogen interactions in active pocket site of transcriptional regulator 1IK3. ADMET analysis also revealed that compound crossing the blood brain barrier that may be involved in its highest percentage LOX inhibition with significant anti-inflammatory properties. Upon comparison of both *in silico* and *in vitro* analysis, it was evident that all compounds presented comparable binding energies to both targets, i.e., 1IK3 and 2UV0 (Tables 7 and 8). However, the binding affinities of few compounds were comparably as high as compound D and compound E, but these did not show activity during *in vitro* analysis. It is known that molecular docking analysis relies on computational screening and the results may [38,39]. In this case, despite hydrogen bond interaction, it could be hypothesized that complexes of compounds A and C and E might be stabilized by other non-covalent forces such as hydrophobic interactions and thus showed more activity compared with other tested molecules.

CONCLUSION

It was detected that compounds A, C and E were appeared to possess biofilm. Inhibitory potential, whereas compound D is potent LOX inhibitor followed by compound E with anti-inflammatory properties. Thus, the antimicrobial, antibiofilm and anti-inflammatory characteristics of the *Prunus persica* L may be related due to the presence of the Polyphenolic constituents.

AUTHORS' CONTRIBUTION

AR, TK, and FS performed analysis and interpretation of enzyme inhibitory data. AHS proposed the project and participated in drafting. MA and AR performed molecular docking and formal analysis. TK and FS participated in drafting and some formal analysis. AR designed the method and the main project, SAR participated in drafting, edited the manuscript, and gave the final approval of the version to be submitted.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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