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ORIGINAL ARTICLE

Molecular Interaction of Naringin and Its Metabolite Naringenin to Human Liver Fibrosis Proteins: An *In Silico* Approach

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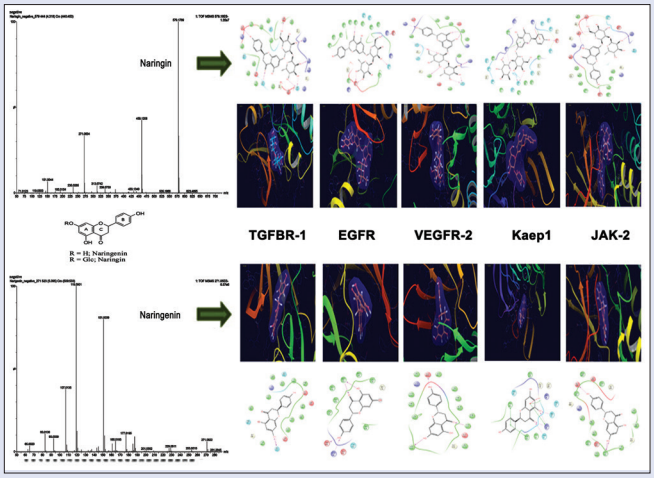
ABSTRACT

Background: Naringin, pharmaceutically active flavonoid, rapidly metabolizes in liver into naringenin. Both naringin and naringenin have significant biological activity and less toxicity. **Objective:** In the present study, *in silico* molecular interactions of naringin and its metabolite naringenin have been evaluated against different human liver fibrosis proteins. **Materials and Methods:** The major human therapeutic protein targets such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor-2 (VEGFR-2), fibroblast growth factor receptor-1 (FGFR1), Kelch-like ECH-associated protein-1 (Kaep1), transforming growth factor beta receptor I (TGFBR-1), angiotensin II receptor type-1 (Angio-II-Type-1), Janus kinase-2 (JAK-2), Zeta-chain-associated protein kinase-70 (ZAP-70) have been selected for the docking studies. This computational study was performed using Schrödinger Suite Maestro 10.3 Glide software 2015. **Results:** The studies demonstrated comparable binding affinities of naringin and naringenin with human therapeutic protein targets such as JAK-2, ZAP-70 Kinase, Angio-II-Type 1, TGFBR1, Kaep1, EGFR, VEGFR-2, and FGFR1 when compared to their respective standard drugs such as gefitinib, regorafenib, dovitinib, bardoxolone methyl, SB-431542, olmesartan, and ruxolitinib. Naringin showed better glide score ranging from −8.5 to −13.3 kcal/mol whereas its metabolite Naringenin also showed comparable glide score ranging from −5.4 to −9.3 kcal/mol. The binding of target proteins with respective standard drugs showed −2.2 to −10.12 kcal/mol. **Conclusion:** The observed *in silico* human protein interactions of naringin and its metabolite naringenin could be exploited for the anti-liver fibrosis therapy. The results derived from this pioneering virtual study may advance further mechanistic *in vitro* and preclinical *in vivo* studies.

Key words: Liver fibrosis, molecular docking, naringenin, naringin

SUMMARY

- Naringin and its metabolite naringenin could interact with different human proteins JAK-2, ZAP-70 Kinase, Angio-II-Type1, TGFBR1, Kaep1, EGFR, VEGFR-2, FGFR1 kinase and subsequently inhibit the progression of liver fibrosis.



Abbreviations used: Jak-2: Janus kinase-2, ZAP-70: Zeta-chain-associated protein kinase-70, Angio-II-type-1: Angiotensin II receptor type-1, TGFBR1: Transforming growth factor beta receptor I, Kaep1: Kelch-like ECH-associated protein-1, EGFR: Epidermal growth factor receptor, VEGFR-2: Vascular endothelial growth factor receptor-2, FGFR1 kinase: Fibroblast growth factor receptor-1.

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INTRODUCTION

Flavonoids are one of the pivotal natural products of interest due to their role in prevention of chronic disorders through dietary supplementation.[1] Naringin is a flavanone glycoside (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside) having several biological and pharmacological properties. It is formed from the flavanone naringenin and the disaccharide neohesperidose. Naringin is abundant in citrus fruits and grapefruit juices which imparts a characteristic bitter taste[2] Herbal medicinal plants such as *Citrus aurantium L.*, *Citrus medica L.* and *Drynaria quercifolia* (L.) J. Smith are a few reported sources of naringin.[3-5] Our group have reported the anti-inflammatory and anti-liver fibrosis property and the presence of naringin, naringenin in *D. quercifolia*.[5,6] Naringin possesses pharmacological activities such as anti-inflammatory,[7] anticancer,[8] bone regeneration,[9] ameliorates metabolic syndrome,[10] modulate oxidative stress,[11] and protect central nervous system diseases.[12] Naringin was found to be nontoxic for Sprague-Dawley rats in oral acute toxicity study, and the no-observed-adverse-effect-level of naringin in subchronic toxicity was >1250 mg/kg/day in rats when administered orally for 6 months.[13] Following an oral administration of naringin to rats, the tissue concentrations after 8 h revealed the presence of naringin in stomach, small intestine, liver and trachea. Whereas, the metabolite

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naringenin was detected in liver, stomach, small intestine, kidney, lung and trachea.[14] In humans, naringin undergoes extensive phase II metabolism to yield an array of conjugated products including naringenin.[15]

Globally, liver diseases including hepatitis B virus and hepatitis C virus infections, alcoholic liver disease, nonalcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma are major causes of illness and death.[16] Liver fibrosis is reversible even at late stage of disease. Hence, the fibrotic stage is significantly important in therapeutic approach of chronic liver diseases.[17] Activation of hepatic stellate cells (HSCs) means transdifferentiation of quiescent, Vitamin-A-storing cells into proliferative, fibrogenic myofibroblasts are the key mechanism of liver fibrosis in experimental and human liver injury.[18] Thus, HSCs activation leads to the formation of profibrogenic myofibroblasts which further initiates the deposition of extracellular matrix formation and stiffness of liver.[19] Multitargeted approach is the most significant strategy for the anti-liver fibrosis therapy, which includes the elimination of the primary cause of injury, inhibition of inflammation, inhibition of scar tissue formation, increasing matrix degradation, inhibiting HSCs activation, or stimulating HSCs apoptosis.[20] Recently, the use of phytochemicals, especially obtained from dietary sources has gained therapeutic importance due to their safety and efficacy.[21]

Molecular docking studies with unexploited molecules give insights to predict the possible drugability in terms of its binding to human target receptor proteins. Such virtual interactions of ligands could possibly truncate the intensive mechanistic *in vitro* and preclinical *in vivo* studies.[22] Recently, Pradeep *et al.*[22] explored the *in silico* binding of a 25 C prodigiosin to human molecular targets such as cyclooxygenase-2, Zeta-chain-associated protein kinase-70 (ZAP-70) kinase, and Janus kinase-3 (Jak-3) kinase.

Multitargeted approach focusing on different pathways is the most promising therapeutic strategy against fibrotic diseases.[23] Hence, in the present study rather than focusing on a single target, following human therapeutic targets are used to screen the drug against liver fibrosis. Tyrosine kinases (TKs) such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor-2 (VEGFR), and fibroblast growth factor receptor-1 (FGFR) have been identified as central mediators in collagen production and potential targets for anti-liver fibrosis therapies.[24] Under normal conditions, cytoplasmic Nrf2 combines with Kelch-like ECH-associated protein (Keap1). Any drug which could dissociate Nrf2-Kep1 combination by Keap1 modification prevents the oxidative stress in liver fibrosis.[25] Furthermore, transforming growth factor beta receptor I (TGFBR-1), Angiotensin II receptor type-1 (Angio-II-Type-1) and JAK-2 are other important therapeutic targets for liver fibrosis therapy.[26]

Literature survey shows the lack of *in silico* studies with naringin and naringenin onto human therapeutic protein targets such as EGFR, VEGFR-2, FGFR1, Kaep1, TGFBR-1, Angio-II-Type-1, JAK-2, and ZAP-70. Hence, we tried virtually to identify the application potential of naringin and its metabolite naringenin against selected human therapeutic protein markers of liver fibrosis.

MATERIALS AND METHODS

Molecular docking study

Molecular docking *in silico* experiments were performed with Schrodinger Glide dock-XP. The Glide-XP scoring function is inferred from the equation; G score = $E_c + E_v + E_b + E_p$, where E_c, E_v, E_b, and E_p are the different energy levels during molecular docking.[27]

Protein preparation

Using Glide, Schrödinger 2015, the ligand-bound protein structures were imported. Final optimizations, minimizations were performed by default settings of Schrödinger Protein Preparation Wizard (PrepWizard). This preparation protocol added hydrogen, built side chains, and loops with missing atoms, optimized the H-bonding network and performed a restrained minimization to get the final précised structure of proteins for docking.

Ligand binding domain

The target human receptors selected in this study were the ligand binding domains (LBD) of Jak-2, ZAP-70, Angio-II-Type-1, TGFBR1, Kaep1, EGFR, VEGFR-2, and FGFR1 kinase-1. All the LBDs were retrieved from the RCSB Protein Data Bank. Table 1 summarizes information on the target receptors used, their Protein Data Bank IDs, polypeptide chains, number of amino acid (aa) residues.

Ligand preparation

The structures of selected ligands were retrieved from PubChem database; naringin (PubChem CID-442428), naringenin (PubChem CID-439246), ruxolitinib (PubChem CID-25126798), olmesartan (PubChem CID-158781), gefitinib (PubChem CID-123631), SB-431542 (PubChem CID-4521392), bardoxolone methyl (PubChem CID-400769), regorafenib (PubChem CID-11167602), and dovitinib (PubChem CID-9886808). Optimized 3D structure with lower energy was prepared by LigPrep Schrödinger using OPLS 2005 force field method. Here, modified the torsions of the ligands, apart from assigning suitable protonation states. For a ligand, 32 stereo-chemical structures were generated with possible states at pH 7.0 ± 2.0.

Receptor grid generation

Receptor grids were calculated for prepared proteins such that various ligand poses bind within the predicted active site during docking. The grid boxes were generated by choosing the co-crystallized ligands in the LBD, and these glide grids were used for the molecular docking with selected ligands used in this study. Grids were generated keeping the default parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 subjected to OPLS 2001 force field. A cubic box of specific dimensions centerd on the centroid of the active site residues (predicted by CASTp) was generated for each receptor. The bounding box was set to 14 Å ×14 Å ×14 Å for docking experiments.

Molecular docking

Glide docking for each ligand was carried out using Glide dock-XP mode. The prepared glide grid of each ligand was individually docked

Table 1: Summary of the human protein targets studied with protein data bank-ID, number of polypeptide chains, and amino acid residue

Protein target with	RCSB PDB-ID	Number of polypeptide chains	Number of amino acids
JAK-2	3KCK	1	313
Angio-II-Type-1	4ZUD	1	410
ZAP-70 kinase	1U59	1	287
TGFBR1	2X7O	5	342
Kaep1	3VNG	1	309
EGFR	2J6M	1	327
VEGFR-2	1YWN	1	316
FGFR1 kinase	5B7V	2	310

PDB: Protein data bank; RCSB: Research Collaboratory for Structural Bioinformatics; JAK-2: Janus kinase-2; Angio-II-Type-1: Angiotensin II receptor Type-1; ZAP-70 kinase: Zeta-chain-associated protein kinase-70; TGFBR1: Transforming growth factor beta receptor I; Kaep1: Kelch-like ECH-associated protein-1; EGFR: Epidermal growth factor receptor; VEGFR-2: Vascular endothelial growth factor receptor-2; FGFR1 kinase: Fibroblast growth factor receptor-1

to the LBD of the target receptor. Final scores were obtained based on energy-minimized poses and represented as Glide score (G-score). The best docked pose with minimum G-score value was given for each ligand.

RESULTS AND DISCUSSION

In silico molecular docking studies

Molecular docking studies were performed to evaluate therapeutic abilities of active molecules naringin and its metabolite naringenin against human molecular targets of liver fibrosis. The results demonstrated promising binding affinity [Tables 2 and 3] against target receptors in terms of docking score compared with standard drugs [Figure 1]. Glide-XP mode evaluated various factors including G score, G energy, H bonding, ligand efficiency, etc. However, G score-the foremost simplified interpretation of molecular docking has been considered for describing the docking efficiency of ligands. G scores (kcal/mol) >7 is considered as affirmative binding of ligand with target receptor.

Table 2: Summary of the extra precision glide docking results of naringin and standard drugs onto the ligand binding domains of human protein targets

Protein target with PDB-ID	Naringin					Docking score of STD	
	Glide XP docking score	Interacting amino acids	Number of H bonds	Pi-Pi	Pi-Cat	Name of STD	Glide XP docking score
JAK-2 (3KCK)	−12.456	GLU-1015 ASP-994 LYS-882 GLU-930 ARG-980	6	-	-	Ruxolitinib	−9.507
Angio-II-Type-1 (4ZUD)	−11.115	SER-109 TYR-113 THR-260 ASP-263 ARG-167	5	1	1	Olmesartan	−8.422
ZAP-70 kinase (1U59)	−12.764	LYS-369 ASP-479 ASP-461 ALA-417	5	-	-	Gefitinib	−8.134
TGFBR1 (2X7O)	−13.27	GLU-245 HID-283 ASN-338 LYS-337 LYS-213 ASP-290	7	-	-	SB-431542	−8.083
Kaep1 (3VNG)	−9.542	ARG-94 SER-234 ASP-68 ARG-59	6	2	1	Bardoxolone methyl	−2.192
EGFR (2J6M)	−8.466	MET-793 LYS-745 ASP-855 ASN-842 ASP-800	6	-	-	Gefitinib	−8.584
VEGFR-2 (1YWN)	−12.057	LYS-866 GLU-883 CYS-917 ARG-1030 ASN-1031 LEU-838 ASN-921	10	-	-	Regorafenib	−10.118
FGFR1 kinase (5B7V)	−12.347	GLU-531 ALA-564 GLU-486 ASN-568 TYR-563	8	-	-	Dovitinib	−6.174

JAK-2: Janus kinase-2; Angio-II-Type-1: Angiotensin II receptor Type-1; ZAP-70 kinase: Zeta-chain-associated protein kinase-70; TGFBR1: Transforming growth factor beta receptor I; Kaep1: Kelch-like ECH-associated protein-1; EGFR: Epidermal growth factor receptor; VEGFR-2: Vascular endothelial growth factor receptor-2; FGFR1 kinase: Fibroblast growth factor receptor-1; STD: Standard drug; XP: Extra precision; PDB: Protein data bank

Table 3: Summary of the extra precision glide docking results of naringenin and standard drugs onto the ligand binding domains of human protein targets

Protein target with PDB-ID	Naringenin					Docking score of STD	
	Glide XP docking score	Interacting amino acids	Number of H bonds	Pi-Pi	Pi-Cat	Name of STD	Glide XP docking score
JAK-2 (3KCK)	−9.190	GLU-898 LEU-932	3	-	-	Ruxolitinib	−9.507
Angio-II-Type-1 (4ZUD)	−8.218	TYR-87 CYS-180	1	1	-	Olmesartan	−8.422
ZAP-70 kinase (1U59)	−8.540	LYS-369 ASP-479	2	-	-	Gefitinib	−8.134
TGFBR1 (2X7O)	−9.329	HID-283	2	-	-	SB-431542	−8.083
Kaep1 (3VNG)	−5.37	ARG-94 SER-42 ARG-59 ASN-61 PHE-256 TYR-251	4	4	1	Bardoxolone methyl	−2.192
EGFR (2J6M)	−7.920	MET-793 ASP-855 LYS-745	4	-	-	Gefitinib	−8.584
VEGFR-2 (1YWN)	−7.436	LEU-838 GLU-883 CYS-917	3	-	-	Regorafenib	−10.118
FGFR1 kinase (5B7V)	−7.152	GLU-531 ALA-564	3	-	-	Dovitinib	−6.174

JAK-2: Janus kinase-2; Angio-II-Type-1: Angiotensin II receptor Type-1; ZAP-70 kinase: Zeta-chain-associated protein kinase-70; TGFBR1: Transforming growth factor beta receptor I; Kaep1: Kelch-like ECH-associated protein-1; EGFR: Epidermal growth factor receptor; VEGFR-2: Vascular endothelial growth factor receptor-2; FGFR1 kinase: Fibroblast growth factor receptor-1; STD: Standard drug; XP: Extra precision; PDB: Protein data bank

Molecular interaction with Janus kinase-2 and angiotensin II receptor type-1

Naringin interacted with JAK-2 (PDB ID-3KCK) and generated a glide score of −12.46, forming six hydrogen bonds with amino acid residues GLU-1015, ASP-994, LYS-882, GLU-930, and ARG-980. The interaction of naringenin with JAK-2 generated a glide score of −9.2 through the formation of three H bonds with amino acid residues GLU-898 and LEU-932. The standard drug ruxolitinib interacted with JAK-2 and generated a glide score of −9.51 [Figures 1 and 2].

Naringin interacted with Angio-II-Type-1 (PDB ID-4ZUD) which resulted a glide score of −11.12, formed five hydrogen bond interactions, one Pi-Pi interaction, one Pi-Cat interaction with amino acid residues SER-109, TYR-113, THR-260, ASP-263, and ARG-167. Naringenin interacted with Angio-II-Type-1 and generated a glide score of −8.22 through one H bond, one Pi-Pi interaction with 2 amino acid residues TYR-87 and CYS-180 whereas standard drug olmesartan generated a glide score of −8.422 [Figures 1 and 2].

Stimulation of angiotensin-II (AngII) type I receptor (AT1R), activation of Jak-2-signal transducer, and activator of transcription (Jak-STAT) signaling pathway[28] are important factors in the development of liver fibrosis. Inhibition of JAK-2 offers a promising therapy for liver fibrosis.[29] Naringin and naringenin showed comparable binding affinity with angiotensine-II-type-1 receptor and JAK-2. Naringin showed better affinity when compared to standard inhibitor drug Ruxolitinib and Olmesartan, respectively, for inhibitors of Jak-2 and Angio-II-Type-1, respectively. Naringenin also has comparable affinity with Jak-2 and Angio-II-Type-1, which was almost comparable to standard drugs. Thus, inhibition of Jak-2 and Angio-II-Type-1 receptor by naringin and naringenin offers promising therapeutic candidates against liver fibrosis.

Molecular interaction with zeta-chain-associated protein kinase-70

The interaction of naringin with ZAP-70 (PDB ID-1U59) formed a glide score of −12.76, with the formation of five hydrogen bonds with amino acid residues LYS-369, ASP-479, ASP-461, and ALA-417. Naringenin interacted with ZAP-70 and generated a glide score of −8.54 through two H bonds with amino acid residues LYS-369 and ASP-479. The standard drug gefitinib interacted with ZAP-70 and could generate a glide score of −8.134 [Figures 1 and 2].

Nuclear factor-kappa B (NF-κB) signaling pathway appears to have a central function in liver homeostasis, pathophysiology, and regulation of the inflammation–fibrosis–cancer axis.[30] In a major pathway of NF-κB activation; depends on endoplasmic reticulum stress which cause NF-κB activation through tyrosine phosphorylation of IκBα, mediated by the TK ZAP-70.[30] Thus, inhibition of ZAP-70 could indirectly inhibit the NF-κB activation.

Molecular interaction with transforming growth factor beta receptor I

Naringin interacted with TGFBR1 (PDB ID-2×7O) and formed a glide score of −13.27, with the formation of seven hydrogen bonds with amino acid residues GLU-245, HID-283, ASN-338, LYS-337, LYS-213, and ASP-290. Naringenin; interacted TGFBR1 with a glide score of −9.33 through two H bonds with amino acid residue HID-283. The standard drug SB-431542 could generate a glide score of −8.08 [Figures 1 and 2].

Naringin and its metabolite naringenin showed comparable molecular affinity towards TGFBR1, which is better than that of standard drug SB-431542. Increased levels of TGF-β in chronic liver diseases activate HSC to myofibroblast and increased hepatocyte cell death, which causes liver fibrosis.[31] Thus, TGF-β signaling pathway is critical for fibrotic

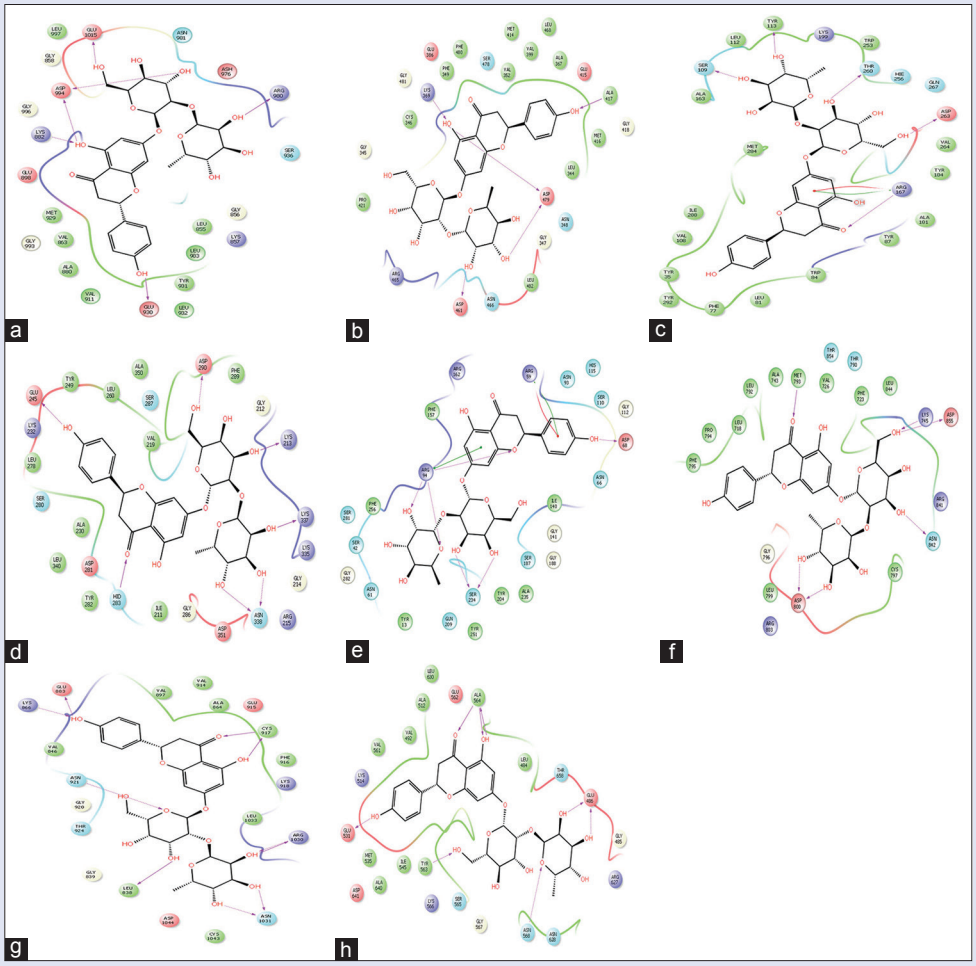

Figure 1: (a) Ligand binding domain of Janus kinase-2 and naringin forming six hydrogen bonds. (b) Ligand binding domain of Zeta-chain-associated protein kinase-70 kinase and naringin formed 5 hydrogen bonds. (c) Ligand binding domain of Angiotensin II receptor type-1 and naringin formed 5 hydrogen, one Pi-Pi, and one Pi-Cat interaction. (d) Ligand binding domain of transforming growth factor beta receptor I, and naringin formed 7 hydrogen bonds. (e) Ligand binding domain of Kelch-like ECH-associated protein-1 and naringin resulting 6 hydrogen, two Pi-Pi, one Pi-Cat interaction. (f) Ligand binding domain of epidermal growth factor receptor and naringin generated 6 hydrogen bonds. (g) Ligand binding domain of vascular endothelial growth factor receptor-2 and naringin formed 10 hydrogen bonds. (h) Ligand binding domain of fibroblast growth factor receptor-1 kinase and naringin formed 8 hydrogen bonds

response in liver, in the classic or canonical pathway, ligand-bound TGFBRII recruits and phosphorylates TGFBR1. Inhibition of TGFB or blocking its downstream signaling pathway resulted in the prevention of the fibrotic process in liver fibrosis.[32] The inhibitory effect of naringin and naringenin on TGF-β signaling through binding with TGFBR1. That is by preventing recruitment, and phosphorylation of Smads, which facilitate TGFBR1 degradation, leading to inhibition of Smad activation.[33]

Molecular interaction with Kelch-like ECH-associated protein-1

Naringin interacted with Kaep1 (PDB ID-3VNG) and generated a glide score of −9.54, with the formation of six hydrogen bonds, two Pi-Pi interaction, one Pi-Cat interaction with amino acid residues such as ARG-94, SER-234, ASP-68, and ARG-59. The molecular interaction of naringenin with Kaep1 produced a glide score of -5.37 through forming four H bonds, four Pi-Pi interactions, and one Pi-Cat interaction with amino acid residues ARG-94, SER-42, ARG-59, ASN-61, PHE-256, and TYR-251. The standard drug bardoxolone methyl could form a low glide score of −2.192 [Figures 1 and 2].

Nuclear translocation of Nrf2 and binding to the site of antioxidant responsive element (ARE) is the key step in the expression of antioxidant defense system.[34] Nrf2 levels are mostly regulated by the complex formation with Kaep1 which dissociate by either Keap1 modification or Nrf2 phosphorylation which activate the Nrf2. The activated Nrf2 translocate into nucleus and interacts with ARE, promoting the expression of cytoprotective target genes responsible for antioxidant defense system;[35] phase II detoxifying enzymes.[36] As naringin and naringenin showed comparable binding affinity with Kaep1 protein, which could cause Keap1 modification and activation of Nrf2. Nrf2 activation is considered as beneficial, especially against liver diseases.[37] Thus, naringin and naringenin may enhance the antioxidant pool through Nrf2/HO-1 pathway.

Molecular interaction with Tyrosine kinases

Molecular interaction with epidermal growth factor receptor

Naringin interacted with EGFR (PDB ID-2J6M) and formed a glide score of −8.46, with the formation of six hydrogen bonds containing amino acid residues MET-793, LYS-745, ASP-855, ASN-842, and ASP-800. Naringenin interacted with EGFR generated a glide score of −7.92

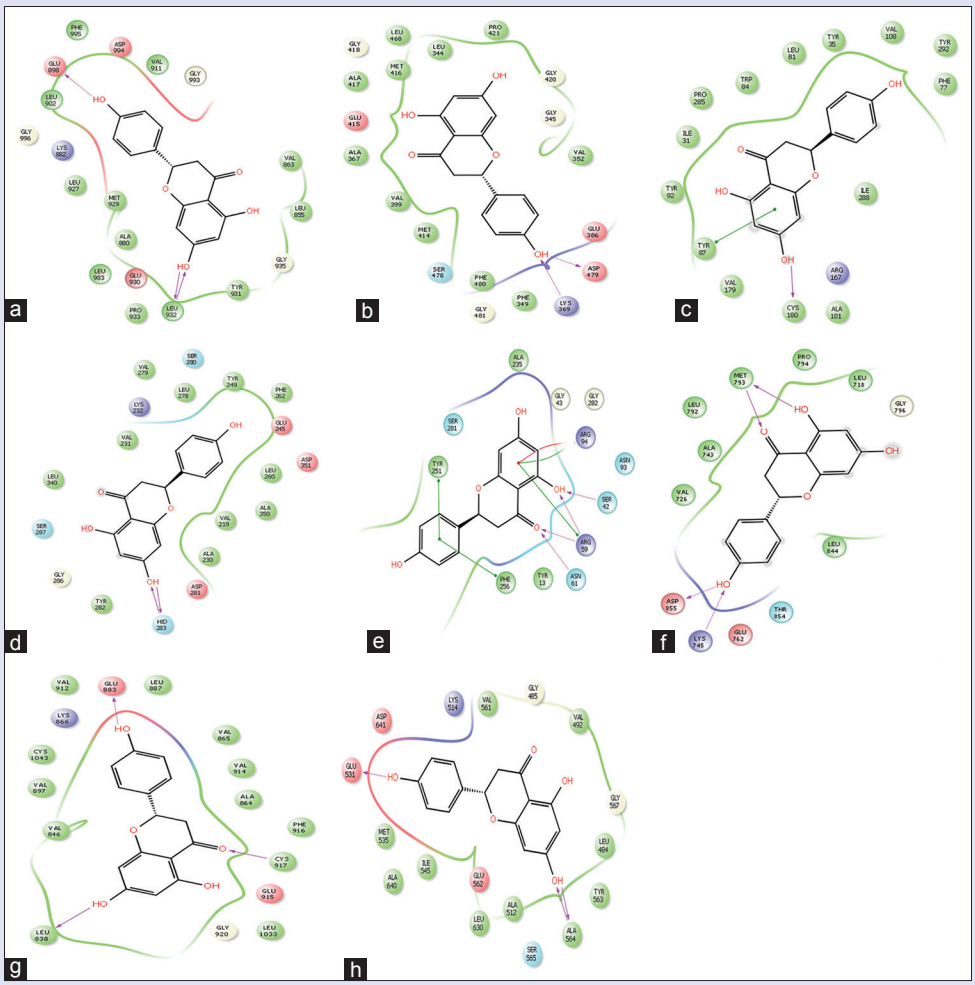

Figure 2: (a) Ligand binding domain of Janus kinase-2 and naringenin resulting 3 H bonds. (b) Ligand binding domain of zeta-chain-associated protein kinase-70 Kinase and naringenin generated 2 H bonds. (c) Ligand binding domain of Angiotensin II receptor type-1 and naringenin formed 1 H bond, one Pi-Pi interaction. (d) Ligand binding domain of Transforming growth factor beta receptor I and naringenin formed 2 H bonds. (e) Ligand binding domain of Kelch-like ECH-associated protein-1 and naringenin formed 4 H bonds, four Pi-Pi, and one Pi-Cat interaction. (f) Ligand binding domain of epidermal growth factor receptor and naringenin formed 4 H bonds. (g) Ligand binding domain of vascular endothelial growth factor receptor-2 and naringenin formed 3 H bonds. (h) Ligand binding domain of fibroblast growth factor receptor-1 kinase and naringenin formed 3 H bonds

through four H bonds with amino acid residues MET-793, ASP-855, and LYS-745. The standard drug gefitinib could generate a glide score of −8.584 while interacting with EGFR [Figures 1 and 2].

Molecular interaction with vascular endothelial growth factor receptor

Naringin interacted with VEGFR-2 (PDB ID-1YWN) and formed a glide score of −12.06, with the formation of ten hydrogen bonds with amino acid residues such as LYS-866, GLU-883, CYS-917, ARG-1030, ASN-1031, LEU-838, and ASN-921. Molecular interaction of naringenin with VEGFR-2 resulted in a glide score of −7.436 through the formation of three H bonds with amino acid residues LEU-838, GLU-883, and CYS-917. The standard drug regorafenib interacted with VEGFR-2 and generated a glide score of −10.118 [Figures 1 and 2].

Molecular interaction with fibroblast growth factor receptor-1

Naringin interacted with FGFR1 (PDB ID-5B7V) resulted a glide score of −12.35, formed eight hydrogen bond interactions with amino acid residues GLU-531, ALA-564, GLU-486, ASN-568, and TYR-563 of FGFR1. Naringenin interacted with FGFR1 with the glide score of −7.152 through three H bonds interacting two amino acid residues GLU-531, ALA-564 of FGFR1. Whereas the standard drug dovitinib generated a glide score of −6.174 [Figures 1 and 2].

TKs play a major role in progression of liver fibrosis. TKs, such as VEGFR-2,[38] platelet-derived growth factor receptor (PDGFR),[39] FGFR1, and EGFR kinases[40] have been identified as central mediators in collagen production and potential targets for anti-liver fibrosis therapies. TK targeting agents exhibit significant inhibitory effects on HSCs activation; downstream signaling pathways MEK/ERK, and PI3K/Akt.[24] As naringin and naringenin showed comparable binding affinities with EGFR, VEGFR, and FGFR which was comparable to standard drugs gefitinib, regorafenib, and dovitinib, respectively, these two natural products could be potent molecules against liver fibrosis.

CONCLUSION

In treatment of liver fibrosis, an effective drug offers hepatocyte protection, anti-inflammatory response, free radical scavenging, and prevents the activation of hepatic stellate cell. Hence, the potent drug against liver fibrosis should target different pathways responsible for liver fibrosis. In this circumstance, our study evaluated the possible molecular

interactions of naringin and its metabolite with different human protein targets responsible for liver fibrosis. Naringin and its metabolite naringenin could interact with human proteins; JAK-2, ZAP-70 kinase, Angio-II-Type 1, TGFBR1, Kaep1, EGFR, VEGFR-2, and FGFR1 kinase which subsequently inhibit liver fibrosis progression through different pathways.

Naringin showed protection against ankylosing spondylitis through the induction of ossification, suppression of inflammation, and oxidative stress and the downregulation of JAK2/STAT3 in mice.[41] Naringin restrained oxidative stress by activating Nrf2 antioxidant pathway.[42] In the present study, the molecular interactions revealed naringin could directly bind with the JAK2 and Kaep1 for the downregulation JAK2/STAT3 and upregulation of Nrf2 respectively.

From the present study, it was clear that naringin and its metabolite naringenin could possibly bind to the multiple human protein targets responsible for the protection of liver from chronic liver diseases. Hence, naringin could be a promising drug candidate for chronic liver diseases along with its well-known pharmacological properties.

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Conflicts of interest

There are no conflicts of interest.

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