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SENOLYTIC ACTIVITY EVALUATION OF CORIANDER (*Coriandrum sativum L*) PHYTOCONSTITUENTS: *In-silico* STUDY

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ABSTRACT

Coriander phytoconstituent has pro-apoptotic and anti-inflammatory activities. This study evaluated the activity of Coriander phytoconstituent against the Senescent Cell Anti-Apoptotic Pathways (SCAPs) network nodes that serve as targets for senolytic drugs. Docking simulations were performed using Autodock Vina PyRx (v0.8), Autodock Tools 1.5.6, and visualized by the Discovery Studio Visualizer. The anti-apoptotic protein (BCL-XL, BCL-2, BCL-W, and survivin) interaction network was obtained from String db.org. The flavonoid compounds showed good binding energy than non-flavonoid compounds. In flavonoid compounds, referring to the binding energy of standard drugs, rutin have a potent affinity to survivin with a binding energy of -7.47 kcal/mol. In addition, the binding energy of galangin-5-methylether, pectolinarigenin, luteolin, apigenin, and 5,6,7-trimethoxyflavone serve higher binding activity to BCL-XL in the ranges -7.73 – -8.64 kcal/mol. Meanwhile, pseudobaptigenin has an affinity to both proteins, survivin, and BCL-XL with the binding energy of -5.71 and -8.64 kcal/mol respectively. Hence, the coriander phytoconstituents could have the potential as a senolytic agent by interfering with the SCAPs, especially BCL-XL and survivin.

Keywords: *Coriandrum sativum L*, Anti-Apoptotic Protein, Senescent Cells, *In-silico*

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INTRODUCTION

Chronic senescent cells contribute to causing some age-related diseases, including cardiovascular disease, neurodegenerative disorders, cancer, type 2 diabetes, kidney-related diseases, cataracts, liver diseases, and metabolic syndrome.[1] Senescent cell secrete the senescence-associated secretory phenotype (SASP) factor and likely contribute to the linking of senescent accumulation with local and systemic dysfunction and disease.[2, 3] The activation of SASP has a beneficial role to eliminated senescent cells and activating immune clearance in acute senescence, otherwise, the released SASP factors sensitize non-senescent neighboring cells to senescence and accumulated according to the declining capacity of senescent cell discarding, especially in elderly people.[4] Senescent cells are resisted the apoptotic process and initiate anti-apoptotic pathways, resulting in senescent cells generating SASP and stimulate destroying the neighboring cells.[5,6] The anti-apoptotic pathways are targeted as senescent cell elimination include Senescent Cell Antiapoptotic Pathways (SCAPs) related to networks of BCL-2 (B-cell lymphoma 2)/BCL-XL (B-Cell Lymphoma extra large) and human inhibitor of apoptosis protein (IAP) family, survivin.[7,8] Senescent cells are a target for senolytic agents that interact on multiple SCAPs network nodes, thereby increasing accessible specificity for senescent cells and diminishing off-target effects on non-senescent cells.[9] The senescent cells could be eliminated pharmacologically as entry points for the treatment of age-related pathologies, and several senolytic drugs that have been studied include dasatinib, navitoclax, and BCL-2 pro-survival family

inhibitors.[9,10] However, an inclination linked with thrombocytopenia from the senolytic drugs such as BCL inhibitors, Navitoclax, brings a limitation from the drugs.[11] Meanwhile, fisetin and quercetin, natural product compounds, have been studied as senolytic and no weakness reported. Some senolytic flavonoids operate by inhibiting BCL-2 relations like BCL-XL and other SCAP network components. Coriander contains some flavonoids and other active compounds.[12] In addition, ranging biological activities of coriander, such as pro-apoptotic, anti-inflammatory, anti-diabetic, and anti-cancer, have been studied.[13-15] Hence, in this current study, we evaluated the activity of coriander phytoconstituents against several anti-apoptotic protein molecules (BCL-XL, BCL-2, BCL-W, and survivin) through *in-silico* study. This study serves as an initial step in elaborating the role of *Coriandrum sativum* as a senolytic agent.

EXPERIMENTAL

PyRx (v0.8), AutodockTools, Discovery Studio Visualizer, and Cytoscape 3.8.2 were performed to study *in-silico*. The 3D protein crystal structures were retrieved from RCSB Protein Data Bank with PDB ID 7LH7 (BCL-XL), 4MAN (BCL-2), 2Y6W (BCL-W), and 3UIH (Survivin). The ligand data obtained from GC-MSs analysis of coriander seeds extract compounds (supplementary data) and the flavonoid compounds of coriander leaves (literature data).[16] The sdf format of ligand structures retrieved from the chemical database PubChem National Center for Biotechnology Information. The docking simulations based on virtual molecular screening were performed using the Autodock Vina tool compiled in PyRx (v0.8).[17] Redocking with AutodockTools 1.5.6 was applied to selected proteins and compounds, to confirm the screening results. The ligand-protein interactions were visualized using the software Discovery Studio Visualizer, including hydrogen bond and hydrophobic interaction. In addition, the data of anti-apoptotic protein interaction was retrieved in string db.

RESULTS AND DISCUSSION

Virtual Screening Result

The activity of coriander phytoconstituent was evaluated against several anti-apoptotic proteins including BCL-XL, BCL-2, BCL-W, and inhibitor apoptotic protein survivin through molecular docking prediction. The docking results from PyRx processing were analyzed based on the binding energies of protein-ligand interaction. Navitoclax and celecoxib were used as controls in this study. Navitoclax is an inhibitor of BCL-XL, BCL-2, and BCL-W, whereas, Celecoxib, an approved FDA drug, is a selective cyclooxygenase-2 (COX-2) inhibitor, inducing apoptosis and suppressing the survivin expression.[18-20]

Table-1: Docking Result of Flavonoid Compounds from PyRx

Protein			BCL-2	BCL-W	BCL-XL	Survivin
Binding energy (kcal/mol)	Flavonoid Compound (Pubchem CID)	Pinobanksin (73202)	-7.1	-7.5	-8.2	-7.6
		Pinocembrin (68071)	-7.5	-7.2	-8.8	-7.2
		Galangin-5-methylether (5488105)	-7.8	-7.4	-9.5	-6.6
		Isorhamnetin-3-O-rutinoside (5481663)	-7.3	-9.4	-9.0	-7.1
		Pectolinarigenin (5320438)	-7.5	-7.6	-9.9	-7.2
		Pseudobaptigenin (5281805)	-7.8	-7.8	-10.0	-7.4
		Daidzein (5281708)	-7.6	-7.2	-9.3	-6.9
		Rutin (5280805)	-8.3	-8.6	-9.0	-7.9
		Quercetin-3-O-glucoside (5280804)	-7.4	-7.3	-8.5	-7.1
		Luteolin (5280445)	-7.7	-7.7	-10.0	-7.8
		Apigenin (5280443)	-7.7	-7.3	-9.6	-7.5
		Quercetin (5280343)	-7.3	-7.2	-8.4	-7.1
		5,6,7-Trimethoxyflavone (442583)	-7.2	-6.8	-9.6	-6.6
		Kaempferol 3,5-dimethyl ether	-7.1	-7.3	-9.1	-6.6
	Standard drugs	Navitoclax (24978538)	-8.1	-9.2	-9.4	-
		Celecoxib (2662)	-	-	-	-7.0

Table-2: Docking Result of Non-Flavonoid Compounds from PyRx

Protein			BCL-2	BCL-W	BCL-XL	Survivin
Binding energy (kcal/mol)	Non-Flavonoid Compound (Pubchem C ID)	Oleic acid (445639)	-5.0	-5.0	-6.7	-5.7
		9,12-Octadecadienoic acid (5280450)	-5.6	-4.7	-7.4	-4.3
		Geraniol Butyrate (5355856)	-5.8	-4.6	-7.2	-6.1
		Geranyl 3-methylbutanoate (5362830)	-6.2	-5.4	-6.7	-4.5
		Ethyl Oleate (5363269)	-5.7	-3.9	-6.7	-4.3
		Methyl-7-Octadecenoate (5364440)	-5.4	-4.8	-7.0	-4.8
		Monoelaidin (5364833)	-5.3	-4.8	-6.8	-5.1
		Grandlure II (5365896)	-5.6	-4.9	-5.5	-4.9
		13-Octadecenal (5367670)	-4.6	-4.3	-6.7	-4.4
		9,12-Octadecadien-1-ol (5462912)	-5.8	-4.3	-7.1	-4.2
		(9E)-9-Octadecenoic acid (637517)	-5.4	-4.4	-6.8	-4.0
		Palmitic acid methyl ester (8181)	-4.7	-3.8	-6.1	-3.7
		9,17-Octadecadienal (6431297)	-5.1	-4.4	-6.7	-4.3
	Standard drugs	Navitoclax (24978538)	-8.1	-9.2	-9.4	-
		Celecoxib (2662)	-	-	-	-7.0

In contrast Table-1 and 2, shows the binding energy of flavonoid compounds improve higher than non-flavonoid compounds. Meanwhile, most flavonoid compounds have a good affinity to BCL-XL ranging in -9.5 to -10.0 kcal/mol and survivin ranging in -7.1 to -7.9 kcal/mol. Therefore, BCL-XL and survivin were used to redocking with AutodockTools to confirm and compare the virtual screening results. In addition, rutin compounds show good affinity to BCL-2, as isorhamnetin-3-O-rutinoside to BCL-W.

Redocking with AutodockTools

Redocking was used benzothiazole, as crystallographic ligand of BCL-XL, which docking grid box was set in grid size x = 82, y = 80, z = 70 and grid center at dimensions (-0.139, -11.969, -1.238). Whereas survivin with PDB ID 3UIH used SMAC, a secondary mitochondrial activator of caspase, a reference crystallographic ligand. Docking grid box was set to grid size x = 34, y = 34, z = 34 and grid centers at dimensions (-32.322, -9.920, 3.059).

Table-3: Docking Result of Compounds from AutodockTools

Protein			BCL-XL	Survivin
Binding energy (kcal/mol)	Compound	5,6,7-Trimethoxyflavone (442583)	-8.54	-
		Apigenin (5280443)	-7.87	-
		Luteolin (5280445)	-7.76	-
		Galangin-5-methylether (5488105)	-7.73	-
		Pectolinarigenin (5320438)	-8.25	-
		Pseudobaptigenin (5281805)	-8.64	-5.71
		Rutin (5280805)	-	-7.47
	Standard drugs	Navitoclax (24978538)	-7.48	-
		Celecoxib (2662)	-	-5.62

Docking result from Table-3 shows the same result in several flavonoids between redocking and virtual screening, such as galangin-5-methylether, pectolinarigenin, pseudobaptigenin, luteolin, apigenin, and 5,6,7-trimethoxyflavone. Meanwhile, pseudobaptigenin has a good affinity with both proteins, BCL-XL, and survivin.

Table-4 and 5 describes the interaction of amino acid residues with the coriander compounds visualized by Discovery Studio Visualizer v21, from virtual screening and Redocking, which give a similar result. One interaction of them is presented in figure 1a. The visualization showed the hydrophobic interacting residues in the hydrophobic groove area of BCL-XL, including PHE105, LEU130, ALA104, ALA142, LEU108,

PHE146, ARG139, and the interacting hydrogen bond residues, ASP107, LEU108, GLU129, and LEU130, were in the binding area of BCL-XL. It was appropriate for Azam *et al.* study.[18] Figure-1b represents the visualization 3D area hydrophobic of BCL-XL.

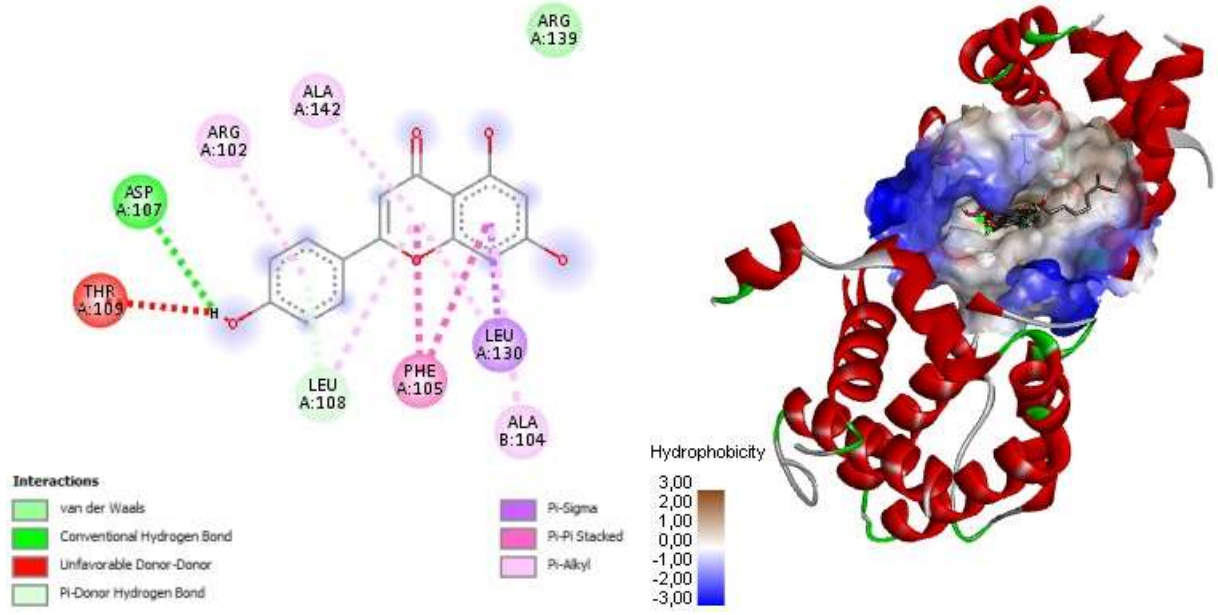
Table-4: Interaction Amino Acid Residues from Virtual Screening Result

Protein	Compound	Conventional hydrogen bond	Hydrogen bond	Hydrophobic
BCL-XL	Galangin-5-methylether	1 (SER106)	1 (LEU108)	PHE105, LEU130, ALA104, ALA142, ARG139, ARG102, LEU108, LEU130
	Pectolinarigenin	1 (GLU129)	2 (LEU130, ASP133)	PHE105, LEU130, ALA104, ALA142, LEU108, ARG102, ALA149
	Pseudobaptigenin	1 (ARG139)	0	PHE105, LEU130, ALA104, ALA142, LEU130, ARG102, ARG139
	Luteolin	0	0	PHE105, LEU130, ALA104, ALA142, LEU108, ARG102, PHE146
	Apigenin	1 (ASP107)	1 (LEU108)	PHE105, LEU130, ALA142, ARG102, LEU108, ALA104
	5,6,7-Trimethoxyflavone	1 (ARG139)	2 (GLU129, LEU130)	PHE105, LEU130, ALA104, ALA142, ARG139, ARG102, LEU108
BCL-2	Rutin	4 (ASP108, ASN140, LEU134, GLU133)	1 (GLU133)	ALA146, ARG143, MET112
BCL-W	Isorhamnetin-3-O-rutinoside	2 (LEU86, ARG95)	1 (GLY89)	ARG95, ALA98, LEU86
Survivin	Isorhamnetin-3-O-rutinoside	4 (HIS80, SER82, LYS110, ASN118)	3 (SER81, LYS115)	ALA114, LYS115
	Pectolinarigenin	0	1 (LEU87)	LYS15, PHE93
	Pseudobaptigenin	1 (ASN118)	0	LYS115, CYS60
	Rutin	3 (GLU36, LYS15, PHE93)	1 (GLN92)	PHE86, ILE74
	Quercetin-3-O-glucoside	6 (ASN111, GLU107, LYS103, LYS110, PHE59, LYS115)	1 (GLY83)	-
	Luteolin	1 (PHE93)	0	ILE74, LEU87
	Apigenin	0	0	ILE74, LEU87
	Quercetin	2 (GLU63, ASN118)	1 (LYS115)	LYS115, LYS62, CYS60

Similarly with the interaction residues result of BCL-XL, the interaction between Smac and survivin appropriate to Sattarinezhad *et al.* study, that observed in LEU54, LEU64, and TRP67 residues in hydrophobic interaction and GLU51, GLU63, GLU65, LYS62, GLU76, ASP71, and HIS80 residues in hydrogen bonds.[21]

Flavonoids are known as bioactive compounds with important biological functions in natural plant compounds and have a beneficial effect on humans by targeting multiple cell systems.[22] Based on the docking result and interaction amino acid residues, several flavonoid compounds could interact with BCL-

XL and survivin. Hence, the coriander phytoconstituents could have the potential as a senolytic agent by interfering with two anti-apoptotic pathways.



(a) (b)

Fig.-1: Representative of visualization 2D and 3D with Discovery Studio Visualizer v21. (a) Hydrophobic and Hydrogen Bonds of Apigenin Compound Interaction, (b) Visualization of 3D Ligands in the Binding Site of BCL-XL protein

Table-5: Interaction Amino Acid Residues from Redocking Result

Protein	Compound	Conventional hydrogen bond	Hydrogen bond	Hydrophobic
BCL-XL	5,6,7-Trimethoxyflavone	1 (ARG139)	2 (LEU130, LEU108)	PHE97, ARG102, PHE105, ALA142, LEU130, ARG139
	Apigenin	3 (ASP107, GLU129, ARG139)	1 (LEU108)	ARG102, PHE105, LEU130, ALA142, ARG139
	Luteolin	3 (GLU129, ARG139, ALA142)	1 (ARG102)	PHE105, ARG102, LEU108, LEU130, ALA142
	Galangin-5-methylether	1 (SER106)	1 (GLU129)	PHE97, ARG102, PHE105, LEU108, LEU130, ALA142, ARG139
	Pectolinarigenin	1 (ARG139)	0	PHE97, ARG102, PHE105, LEU108, LEU130, ALA142, ARG139, PHE146
	Pseudobaptigenin	1 (ASP107)	1 (LEU108)	ARG102, PHE105, LEU108, LEU130, ALA142, ARG139
Survivin	Pseudobaptigenin	2 (GLU65, ASP71)	0	LEU64, TRP67
	Rutin	5 (GLU51, GLU65, GLY66, ASP71, GLU76)	HIS80	HIS80

It is visualized in from string db and shown in Fig.-2, which describes the interaction between survivin, BCL-2, and BCL-XL. The interaction is connected by cellular tumor antigen p53 (TP53). In addition, BIK and BAD, pro-apoptotic proteins interconnect between BCL-XL, BCL-2, and BCL-W.

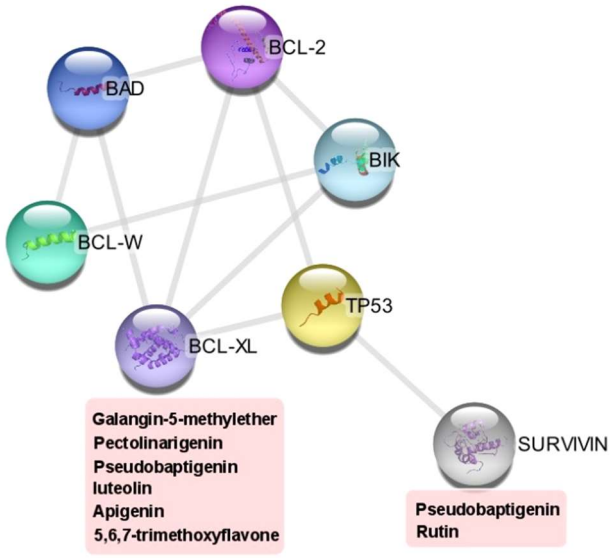


Fig.-2: Interaction of BCL-XL, BCL-2, BCL-W, and Survivin Protein with Coriander Compounds

CONCLUSION

In summary, docking results showed that flavonoid compounds have a good performance than non-flavonoid compounds. Galangin-5-methyl ether, pectolinarigenin, pseudobaptigenin, luteolin, apigenin, and 5,6,7-trimethoxyflavone performed good binding activity with BCL-XL, whereas rutin and pseudobaptigenin, showed good binding activity with survivin. In addition, pseudobaptigenin has potential activity as an inhibitor of anti-apoptotic protein, due to its binding activity to BCL-XL and survivin. It could be hypothesized that the phytoconstituent of *Coriandrum sativum* interferes with Senescent Cell Antiapoptotic Pathways (SCAPs) and has a potential effect as a senolytic agent to reduce senescent cells, however, it should be proved *in-vitro* and *in-vivo* studies.

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