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FULL PAPER

In silico molecular docking study from *Moringa oleifera* and *Caesalpinia sappan* L. secondary metabolites as antagonist TRPV1

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One of the classifications of peripheral neuropathy causes is due to the use of chemotherapeutic agents called chemotherapy-induced peripheral neuropathy (CIPN) conditions. Administration of platinum groups resulted in changes in the expression and function of Transient Receptor Potential Vanilloid type 1 (TRPV1) as well as altered neuronal excitation and propagation of nociceptive sensory signals. *Moringa oleifera* and *Caesalpinia sappan* L. are reported for their neuroprotective effect. In this study, we conducted a molecular docking study for 63 secondary metabolites of *Moringa oleifera* and 27 secondary metabolites of *Caesalpinia sappan* L. using an *in silico* approach targeting TRPV1 (PDB ID: 5IS0) using AutoDockVina software. ADMET characteristics were predicted using the SwissADME and pkCSM Online Tool. This study found that the binding energy of the six metabolites of *Moringa oleifera* (quercetin, ellagic acid, lutein, luteolin, rhamnetin, and 3-O-beta-D-Glucopyranosyl sitosterol) and three metabolites of *Caesalpinia sappan* L. (ombuin, phanginin I, and phanginin J) lower than native ligand through TRPV1 protein. This compounds are potential to be developed as a candidate for antagonist TRPV1. Furthermore, this study became basic data for developing TRPV1 antagonist-targeted therapy, especially in CIPN conditions.

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Introduction

Neuropathic pain is associated with various conditions and syndromes due to central or peripheral nervous system damage [1].

One of the causes of peripheral neuropathy is due to the use of chemotherapeutic agents. The incidence of chemotherapy-induced peripheral neuropathy (CIPN) in patients undergoing cancer treatment is about 30-40% [2], and the platinum group has the most remarkable prevalence rate, up to 70% [3].

There are several clinically recommended drugs for neuropathic pain, such as tricyclic antidepressants (TCAs), calcium channel α2-δ ligands, serotonin-norepinephrine reuptake inhibitors (SSRIs), and topical lidocaine [4,5].

It is known that most therapeutic options bring additional problems related to side

effects and the lifelong use of drugs due to their lack of contribution to prevent disease progression. Thus, further study to reveal the key signaling pathway in the progression of CIPN and explore new therapeutic approaches is still needed.

In recent years, transient receptor potential vanilloid type 1 (TRPV1) antagonists have been widely studied to develop treatments for various diseases, particularly those related to neurogenic pain and inflammation, such as anti-inflammatory, antineoplastic, and antinociceptive [6-8]. According to the increasing evidence, TRPV1 plays an important role in the CIPN progression. Platinum compounds, such as cisplatin and oxaliplatin, alter the expression and function of TRPV1 in rat DRG neurons [9,10].

The increased reactive oxygen species (ROS) production directly activates TRPV1 channels [11].

TRPV1 activation in the DRG alters neuronal excitation and the propagation of nociceptive sensory signals [12].

Previous findings confirm that TRPV1 activation causes chronic pain through depolarization and stimulation of the NMDA receptor subunit NR2B (NMDAR2B) in the dorsal horn of the spinal cord [13,14].

Furthermore, TRPV1 inhibition potentially suppresses the progression of neuropathic pain [15,16].

Moringa oleifera is a medicinal plant distributed in many tropical regions. Studies on the pharmacological activity of *Moringa oleifera* have been reported its anti-inflammatory, analgesic, antioxidant, anticancer, hepatoprotective, neuroprotective, antidiabetic, and antimicrobial effects [17,18].

Active phytochemicals found in Moringa oleifera include specific glucosinolates, carotenoids, flavonoids and phenolic acids, polyunsaturated fatty acids, minerals, tocopherols, and folate [19]. Previous studies show that *Moringa oleifera* leaves extract exhibits an antinociceptive effect confirmed through hot-plate, writhing, formalin tests [20], tail flick, and tail immersion tests in rats [21].

The ethanolic extract of *Moringa oleifera* also shows an antinociceptive effect on vincristine-induced peripheral neuropathy, possibly by suppressing the levels of proinflammatory cytokines such as IL-6, TNFα, and IL-1β [22].

Caesalpinia sappan L., a member of the Fabaceae family (subfamily Caesalpinioideae), is reported to be pharmacologically active as an anticancer, antimicrobial, antiparasitic, anti-inflammatory, antiarthritic, neuroprotection agent [23].

Caesalpinia sappan L. is often used for its stem bark and it is reported to contain bioactive ingredients such as protosappanin, brazilin, chalcone, xanthones, flavones, and homoisoflavonoids [24].

In addition, it is reported that *Caesalpinia sappan* L. extract exhibits an antinociceptive effect confirmed by *in vivo* writhing test [25].

The findings above demonstrate that *Moringa oleifera* and *Caesalpinia sappan* L. are potential plant resources for developing new therapeutic compounds for neuropathic pain.

However, there needs to be more studies elaborating on the meaningful molecular interaction between secondary metabolites of the *Moringa oleifera* and *Caesalpinia sappan* L. and TRPV1 channel. Therefore, *in silico* screening using TRPV1 nociceptor channels as a molecular target was conducted to evaluate the activity of secondary metabolites *Moringa oleifera* and *Caesalpinia sappan* L. in inhibiting TRPV1 activity so that may modulate the progression of CIPN conditions. In this study, molecular docking was carried out on the secondary metabolites of *Caesalphinia sappan* L. and *Moringa oleifera*. Molecular docking was also used to investigate the interactions between protein and ligand and the appropriate conformation

of compounds in the prepared protein. In addition, physicochemical and toxicity analyzes were utilized to obtain compounds that met the physicochemical criteria.

Experimental

Ligand and protein preparation

The structure of TRPV1 protein was downloaded on https://www.rcsb.org in Protein Data Bank (PDB) format code 5IS0 (chain A). Protein preparation was performed using AutoDockTools version 1.5.6 and was saved as PDBQT. Meanwhile, the list of test ligands were the secondary metabolites of *Caesalpinia sappan* L. and *Moringa oleifera* obtained from KNApSAcK data (http://www.knapsackfamily.com).

All SMILES formats of test ligands were downloaded from PubChem website (http://pubchem.ncbi.nlm.nih.gov). OpenBabel online was used to convert the ligands from SMILES into PDBQT format. Docking protocol validation was analyzed using PyMOL software version 4.6.0 (Schrödinger LLC).

Molecular docking and visualization

All procedures were performed using the software Windows 11 Home Single Language 64-bit operating system Intel (R) Core (TM) i3-1005G1 CPU @ 1.20GHz (8 CPUs), ~1.20 GHz. The grid box for 5IS0 receptor was 18 Å×18 Å×18 Å, centered at 107.52 94.061 101.735. The docking protocol validity is accepted if the value of root mean square deviation (RMSD) less than equal to 2.0 Å. Molecular docking simultaneously on multiple ligands was performed using the Cygwin command to operate AutoDock Vina and obtain binding energy prediction value. Ligand-protein interactions were visualized using Biovia Discovery Studio Visualizer v21.1.0.20298 software (Dassault Systèmes, San Diego, California, USA). To find out the physicochemical properties and toxicity of the test ligand as a candidate for drug ingredients using SwissADME (http://www.swissadme.ch/index.php) and pkCSM (https://biosig.lab.uq.edu.au/pkcsm/prediction)

Results and discussion

According to the analysis of predicted binding affinity, the binding energy of the top list 7 of 63 metabolites from *Moringa oleifera* and 4 of 27 from *Caesalpinia sappan* L. were lower than capsazepine as a native ligand (Table 1). The affinity of ligand bonds with receptors is correlated with the binding energy [26]. The binding energy value reflects the amount of energy the ligand needs to bind to a receptor. The stronger the bond between the ligand and receptor, the lower the binding energy and the more negative value.

Based on the present study, among the 63 *Moringa oleifera* metabolites compounds tested, quercetin showed the lowest binding energy (-7,80 kcal/mol), followed by ellagic acid with a binding energy of -7,50 kcal/mol. Apigenin, lutein, luteolin, rhamnetin (-7,40 kcal/mol), and 3-O-beta-D-Glucopyranosyl sitosterol (-7,20 kcal/mol) exhibited lower binding affinity than native ligand capsazepine. Similarly, among 27 metabolites of *Caesalpinia sappan* L., ombuin showed the lowest binding energy (-7,50 kcal/mol), followed by phanginin I and protosappanin E-2 (-7,30 kcal/mol), and phanginin J (-7,20 kcal/mol). Other compounds not listed in Tabel 1 presents a higher binding energy prediction than native ligands, indicating a weaker binding affinity.

The receptor-ligand intermolecular interactions are displyaed in Figure 1.

TABLE 1 Secondary metabolites docking scores against TRPV1 (5IS0)

Source	Compound	ΔG (kcal/mol)
Native Ligand	Capsazepine	-7,1
Moringa oleifera metabolites	Quercetin	-7,8
	Ellagic Acid	-7,5
	Apigenin	-7,4
	Lutein	-7,4
	Luteolin	-7,4
	Rhamnetin	-7,4
	3-O-beta-D-Glucopyranosyl sitosterol	-7,2
Caesalpinia sappan metabolites	Ombuin	-7,5
	Phanginin I	-7,3
	Protosappanin E-2	-7,3
	Phanginin J	-7,2

Moreover, the results showed that all of the top 7 molecular docking results of *Moringa oleifera* metabolites and the top 4 of *Caesalpinia sappan* L. metabolites meet Lipinski's rule of five (RO5), except lutein and protosappanin E-2 (Table 2).

The RO5 term represents a molecular weight of less than 500 Da, a log P of less than 5, an H-bond donor of less than 5, and an H-bond acceptor of less than 10. RO5 is used to classify the phytochemicals that are effective in being used as oral drugs [27]. It means that violation of the RO5 leads to poor membrane permeation and absorption. The LD50 parameter is used to measure the relative toxicity of the compound, while hepatotoxicity is associated with compound-induced liver damage.

The pkCSM analysis showed that only capsazepine as a native ligand was predicted to have a hepatotoxicity effect. This result means that the potential compounds from *Moringa oleifera* and *Caesalpinia sappan* L. with lower binding energy than the native ligand and passed the RO5 were non-hepatotoxic.

TABLE 2 Physicochemical properties, drugability, and safety prediction of the compounds

Compounds	Physicochemical Properties					Drug-likeness			Toxicity	
	MW (g/mol)	RBN	HBA	HBD	mLogP	BA Score	Vio-lation	RO5	LD_{50}	Hepatotoxicity
Capsazepine	376,9	5	2	3	2,87	0,55	0	Yes	2,460	Yes
***M. oleifera* metabolites**										
Quercetin	302.19	0	8	4	0,14	0,55	0	Yes	2,399	No
Ellagic Acid	270.24	1	5	3	0,52	0,55	0	Yes	2,450	No
Apigenin	568.87	10	2	2	6,96	0,17	2	No	3,491	No
Lutein	286.24	1	6	4	0,03	0,55	0	Yes	2,455	No
Luteolin	316.26	2	7	4	-0,31	0,55	0	Yes	2,453	No
Rhamnetin	576.85	9	6	4	3,96	0,55	1	Yes	2,376	No
3-O-beta-D-Glucopyranosl sitosterol	302.19	0	8	4	0,14	0,55	0	Yes	2,399	No

***C. sappan* L. metabolites**

Ombuin	330,29	3	7	3	-0,07	0,55	0	Yes	2,272	No
Phanginin I	344,44	3	4	0	2,9	0,55	0	Yes	2,366	No
Protosappann E-2	586,54	1	11	7	0,74	0,17	3	No	2,496	No
Phanginin J	358,43	4	5	0	1,98	0,55	0	Yes	2,396	No

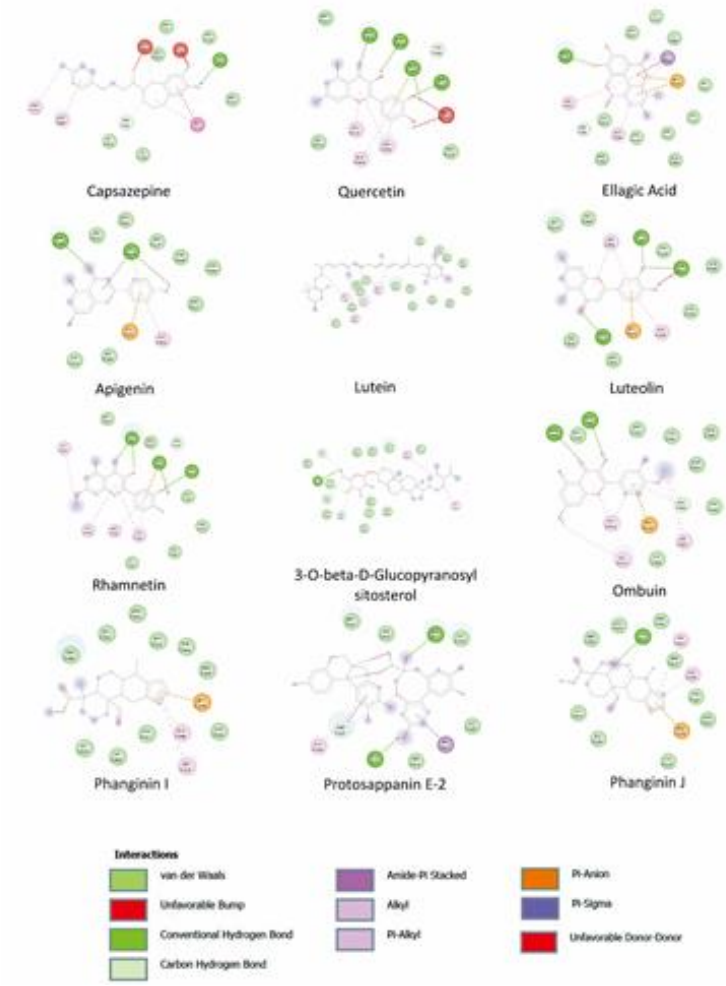

FIGURE 1 The ligand interactions toward 5IS0, TRPV1 receptor. Visualization results were obtain using Biovia Discovery Studio Visualizer v21.1.0.20298 software

Neuropathic pain therapy aims to improve the patient's quality of life. Several different treatments for neuropathic pain have been utilized. Compounds derived from natural products are frequently a source of inspiration in drug discovery, including neuropathic pain.

Through this study, we screened and evaluated several secondary metabolites from *Moringa oleifera* and *Caesalpinia sappan* L. as TRPV1 antagonists. This study evaluates the potential of *Moringa oleifera* and *Caesalpinia sappan* L. secondary metabolites in modulating TRPV1 (5IS0). The docking method is used to determine the ability of metabolites to bind TRPV1 as the pain receptor target to prevent neuropathic progression. The structure of the 5IS0 macromolecule is TRPV1 in complex with capsazepine, its native ligand. Capsazepine,

the first synthetic analog of capsaicin, acts as a TRPV1 antagonist [28].

The validation of binding was done by calculating the RMSD of native ligand and ligand conformation. This result showed that the docking protocol is acceptable because the RMSD value is less than equal to 2 Å.

Interestingly, there have been previous studies regarding the activity of several compounds from neuropathic pain in various models, although few were specific to TRPV1. A study reported that quercetin prevents the increase of thermal and mechanical nociceptive response caused by oxaliplatin and paclitaxel [29,30]. Moreover, quercetin inhibited the increased expression of PKC and TRPV1 in paclitaxel-treated rats and mice spinal cords and DRGs [30].

TRPV1 function is altered by PKCε activation in DRG neurons, contributing to hyperalgesia [31].

Quercetin repaired neuropathic pain in a chronic constriction injury (CCI) rat model by reducing TNF-, IL-6, and IL-1 levels and inhibiting p-38 MAPK, p-ERK, and p-JNK [32].

Quercetin exerted its analgesic effect by inhibiting cytokine-induced inflammatory hypernociception (e.g., TNF and CXCL1) and decreasing carrageenin-induced IL-1 production as well as carrageenin-induced decrease in reduced glutathione (GSH) levels [33].

In addition, Quercetin inhibited peripheral nociceptive muscle pain by inhibiting myeloperoxidase and N-acetyl-β-D-glucosaminidase activities, cytokine production, oxidative stress, and cyclooxygenase-2 expression [34].

Ellagic acid also has an antinociceptive effect and contributes to improve neuropathic pain. Ellagic acid directly protected the peripheral nerves in the diabetic neuropathic mice model and also through the opioidergic system and L-arginine–NO–cGMP–ATP sensitive K+ channels pathway [35-37].

TRPV1 is often coexpressed with MOR1, a member of the GPCR opioidergic system, in the peripheral nervous system such as DRG [38]. TRPV1 is a physiological regulator of MOR1 by regulating MOR1 function via GRK5 [39,40].

In inflammatory pain conditions, TRPV1 inhibition is associated with activating the cGMP/PKG/ATP-sensitive potassium channel signaling pathway [41].

Previous studies have shown that the therapeutic management of neuropathic pain by luteolin acts as an antioxidant, leading to increased expression of antioxidant enzymes, such as SOD, CAT, glutathione peroxidase, and GSH [42]. The same antioxidant effect occurs due to using apigenin and lutein with their mechanism of preventing damage to myelin and axons [43,44].

However, no studies are exploring the activities of rhamnetin, 3-O-beta-D-Glucopyranosyl sitosterol, ombuin, phaginin I, protosappanin E-2, and phaginin J on neuropathic pain. Therefore, the findings in this *in silico* study are potential for further studies.

In vitro and *in vivo* studies, pharmacokinetics, and bioavailability of compounds are needed to ensure the potency of secondary metabolites of *Moringa oleifera* and *Caesalpinia sappan* L.

Conclusion

In silico molecular docking study from *Moringa oleifera* and *Caesalpinia sappan* L. secondary metabolites were conducted. This study concludes that six metabolites of *Moringa oleifera* (quercetin, ellagic acid, lutein, luteolin, rhamnetin, and 3-O-beta-D-Glucopyranosyl sitosterol) and three metabolites of *Caesalpinia sappan* L. (ombuin, phanginin I, and phanginin J) potential to be developed as a candidate for inhibit TRPV1, based on binding energy, RO5, and ADMET results. Furthermore, this study became basic data for developing TRPV1 antagonist-

targeted therapy, especially in CIPN conditions.

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Conflict of Interest

We have no conflicts of interest to disclose.

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