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Potential Activity Of Secondary Metabolites Of Kawista (Limonia Acidissima) As Neurodegenerative Diseases : A Network Pharmacology Approaches

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ABSTRACT

Kawista (Limonia acidissima) is a tropical plant traditionally used in South and Southeast Asian medicine, and its known for its rich nutritional profile and bioactive compounds. This study explores the therapeutic potential of kawista for neurodegenerative diseases. This study aims to investigate the potential of kawista in managing neurodegenerative through a pharmacological network approach. Proteins that can interact with secondary metabolites of kawista were predicted using SwissTargetPrediction, proteins related to neurodegenerative were obtained from GeneCards. The intersecting results were analyzed using STRING with GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment methods. From 47 secondary metabolites of kawista, 218 neuro-related proteins was identified potentially interacting with kawista's secondary metabolites. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and disease-gene association analyses highlighted key biological processes, molecular functions, cellular components, and pathways relevant to neurodegenerative disease mechanisms. The findings suggest that kawista's bioactive compounds could modulate critical pathways and receptor activities, offering insights into developing novel, effective therapies for neurodegenerative disorders. This research providing a scientific basis for kawista-based therapeutic strategies aimed at improving neurodegenerative disease outcomes.

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INTRODUCTION

Kawista (*Limonia acidissima*) is a tropical plant traditionally used in medicine in various South and Southeast Asian countries. The kawista fruit is known for its rich nutritional content. The kawista fruit is known for its rich nutritional content, containing bioactive compounds such as flavonoids, alkaloids, phenols, terpenoids, saponins, and tannins, which have the potential as therapeutic agents (Dhakar et al., 2019). These compounds are believed to have various

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pharmacological effects, including anticancer, antioxidant, antibacterial, antidiabetic, hepatoprotective, and neuroprotective activities (Parvez & Sarker, 2021; Thakur et al., 2020). Despite the promising pharmacological properties of kawista, there remains a gap in comprehensive studies specifically focusing on its neuroprotective potential and mechanisms of action in the context of neurological diseases.

Neurological diseases, such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, pose significant challenges due to their substantial socio-economic burden on society. These diseases are characterized by progressive degeneration of nerve cells, leading to a decline in cognitive and motor functions (Savelieff et al., 2019). Despite extensive research, no therapy is truly effective in halting or reversing this degenerative process (Franco & Cedazo-Minguez, 2014). This underscores the urgent need for novel therapeutic approaches that can offer better outcomes. Exploring natural sources, like kawista, could provide innovative solutions to this pressing issue.

Network pharmacology is an approach that combines pharmacological data with molecular interaction networks to identify the mechanisms of action of compounds on molecular targets in the body (Chandran et al., 2017). This approach allows for a more comprehensive analysis of how bioactive compounds interact with various proteins, enzymes, and genes involved in the pathophysiology of diseases (Ihya et al., 2024). Previous studies have shown that the methanol extract of kawista can improve behavioral parameters in rats, indicating its potential neuroprotective effects (Rakhunde et al., 2014). Specifically, flavonoids in kawista have been demonstrated to reduce oxidative stress and inhibit inflammatory pathways, which are crucial in preventing nerve damage (Mukta et al., 2023). However, more research using network pharmacology is needed to map these complex interactions and fully understand the therapeutic potential of kawista in neurological diseases.

By integrating the pharmacological network approach, this research aims to explore further the potential of kawista in treating neurological diseases. This study will use network pharmacology to map molecular interactions, identify new molecular targets, and understand the mechanisms of action of bioactive compounds in kawista. Through this comprehensive analysis, we aim to uncover novel insights into how kawista compounds can be utilized to develop more effective and safe therapies for neurodegenerative diseases.

In summary, this research will significantly contribute to the field of pharmacology and medicine by addressing the gaps in previous studies and providing a solid scientific basis for developing kawista-based therapies. Our focus on the neuroprotective potential of kawista, utilizing network pharmacology, aims to pave the way for new solutions for neurodegenerative diseases, which currently lack effective treatments.

METHODS

This research adopts an experimental approach that integrates several online tools to explore the interactions between secondary metabolites in Limonia acidissima and their potential therapeutic targets (Hentu et al., 2024). The study utilized various web servers, including Pub Chem(https://pubchem.ncbi.nlm.nih.gov/),SwissTargetPrediction(http://swisstargetpredictio

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n.ch/),GeneCards(https://www.genecards.org/),Venny(https://bioinfogp.cnb.csic.es/tools/venny/), and STRING (https://string-db.org/). The list of secondary metabolite compounds used in this study was founded in the literature (Murthy & Dalawai, 2020). Each secondary metabolite compound's SMILES code was retrieved from PubChem (S. Kim et al., 2023), and then entered into SwissTargetPrediction to predict the proteins that might interact with these secondary metabolites (Daina et al., 2019). Subsequently, neuro-related proteins were identified using GeneCards (Safran et al., 2022), and the intersections between the predicted targets from SwissTargetPrediction and the neuro-related proteins from GeneCards were determined using Venny (Oliveros, 2015). The resulting protein intersections were analyzed using STRING (Szklarczyk et al., 2023) to elucidate the pharmacological network between proteins that are predicted to interact with the secondary metabolite compounds in kawista and neurodegenerative diseases. The resulting data from STRING was further analyzed using Gene Ontology (GO) (Aleksander et al., 2023), Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2023), and disease-gene associations (DISEASES) enrichment (Y. Kim et al., 2022). This methodical approach aims to provide a comprehensive understanding of the potential therapeutic effects of secondary metabolites in kawista. By integrating data from various studies and utilizing advanced online tools, this research strives to map the complex interactions between bioactive compounds and molecular targets, thereby offering insights that could inform the development of new therapeutic strategies.

RESULTS AND DISCUSSIONS

From the literature, 47 secondary metabolites of kawista were used in this research (Table 1). This secondary metabolite was distributed in some parts of the plant. 17 secondary metabolites were found in fruits, 30 in stems, 12 in roots, and 5 in leaves (Murthy & Dalawai, 2020). From these secondary metabolites, it was found that 629 proteins with probability values more than 0 were found using SwissTargetPrediction (Susanto et al., 2023). Those proteins were predicted to interact with secondary metabolites of kawista. 2028 neuro-related proteins were also found at GeneCards. Using Venny, 218 proteins were found intersected (Figure 1). Those proteins were neuro-related proteins that predicted could interact with the secondary metabolite compound of kawista.

Table 1. List of secondary metabolites of kawista (Murthy & Dalawai, 2020)

No	Compound Name	Parts of The Plant
1	2,6-Dimethoxy benzoquinone	(1)
2	3-Formylindole	(2)
3	4-Hydroxybenzoic acid	(1)
4	4-Methoxy-1-methyl-2-quinolone	(2)
5	4-Methoxy-2-quinolone	(2)
6	5-(3-Acetoxypropenyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3- dihydroxybenzofuran-3-ylmethyl acetate	(2)

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No	Compound Name	Parts of The Plant
7	5-Hydroxy-2-(-hydroxyphenyl)-7-methoxy-6-(3-methylbut-2-enyl)chroman-4-one	(4)
8	Acidissimin	(1, 4)
9	Acidissiminol	(1)
10	Acidissiminol epoxide	(1)
11	Aurapten	(4)
12	Bergapten	(1-4)
13	Columbianetin	(2)
14	Demethylsuberosin	(1-2)
15	Dihydrosuberenol	(4)
16	Dihydroxyacidissiminol	(1)
17	Edulitine	(2)
18	Gallic acid	(1)
19	Gallocatechin	(1)
20	Hederatriol	(2)
21	Isopimpinellin	(1, 2, 4)
22	Limodissimin A	(2)
23	Limonin	(2)
24	Lupeol	(2)
25	Marmesin	(2)
26	Marmesin	(4)
27	N, N-dimethyltryptamine	(2)
28	N-benzoyltyramine	(1)
29	Obacunone	(2)
30	Orientin	(3)
31	Osthenol	(1, 2, 4)
32	Osthol	(4)
33	Physcion	(2)
34	Psoralen	(1, 2, 4)
35	Rutaevin	(2)
36	Saponarin	(1, 3)
37	Seselin	(2)
38	Stigmasterol	(2-4)
39	Suberenol	(2)
40	Syringaldehyde	(2)
41	Syringaresinol	(2)
42	Tanakamine	(2)
43	Tanakine	(2)
44	Tembamide	(2)

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No	Compound Name	Parts of The Plant
45	Vitexin	(1, 3)
46	Xanthotoxin	(1, 2, 4)
47	Yangambin	(2)

*Note : (1)Fruit; (2)Stem; (3)Leaf; (4)Root.

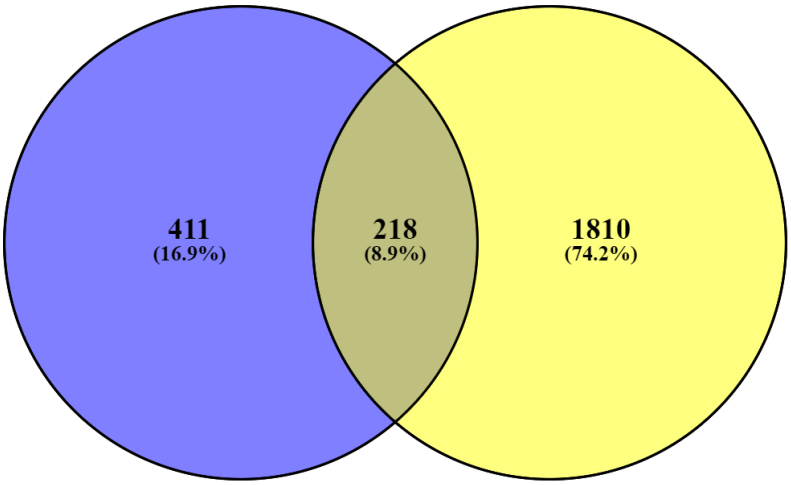

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Figure 1. Venn diagram of proteins that predicted can be interacted with kawista (blue) and neuro-related proteins (yellow)

Network pharmacology was built using STRING (Figure 2), an online database and tool that has more than nine million proteins from various sources and some network pharmacology enrichment analysis (Saputro et al., 2023; Szklarczyk et al., 2023). According to the analysis, this network has 217 nodes and 3210 edges. The node is a disease, target, or drug, and the edge is a known connection between two nodes (Chandran et al., 2017). In this research, the node is a protein target predicted to interact with the secondary metabolite of kawista. From further analysis, this network was expected to have 1261 edges. This means these proteins interact more with themselves than expected for a random set of proteins of the same size and degree distribution drawn from the genome. Such an enrichment indicates that the proteins are at least partially biologically connected (Szklarczyk et al., 2023).

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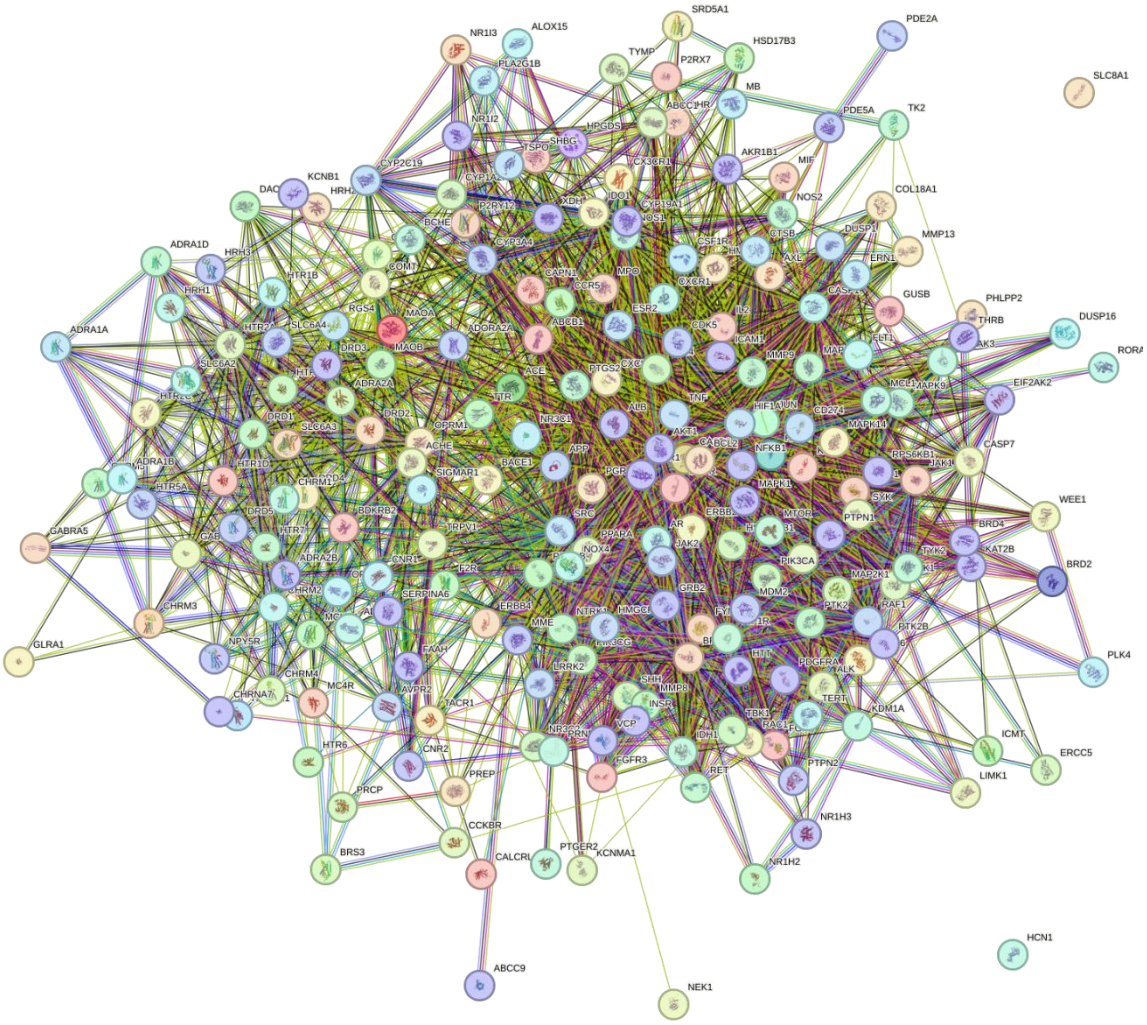

Figure 2. Network pharmacology results using STRING. Circle shown the nodes of network and edge are lines that connect two nodes.

A technique for comprehending biological systems based on a group of genes or proteins obtained from study data is called gene ontology (GO) enrichment. Biological process (BP), molecular function (MF), and chemical component (CC) are the three terminologies utilized in GO (Aleksander et al., 2023). A collection of biological signaling pathways that have been manually drawn to represent knowledge about networks of molecular interactions and reactions is known as KEGG (Kanehisa et al., 2023). DISEASES is a network-based approach and a systematic analysis tool successfully applied to identify disease-related genes in various disorders (Y. Kim et al., 2022). The False Discovery Rate (FDR) value, or the quantity of potential data that could provide a false positive value that is anticipated to be rejected, serves as the foundation for the analysis's conclusions. Accordingly, the analyst results are more accurate and lower the FDR value (Zhong et al., 2004). The FDR in this study is expressed as -Log (p-values); the lower the -Log (p-values) number, the less likely an error is (Figure 3).

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Figure 3. Graph analysis of GO, KEGG, and DISEASES enrichment

The biological processes identified, such as response to chemicals, regulation of signalling, and cellular response to stimuli, are crucial for neuron function and survival. These processes help neurons react to environmental changes and communicate properly (Cho et al., 2023). In neurodegenerative diseases, these processes often become disrupted, leading to problems in how neurons function and communicate (Muddapu et al., 2020). For example, neurons might not respond correctly to signals or fail to regulate critical cellular activities, contributing to the progression of diseases like Alzheimer's and Parkinson's (Maiti et al., 2017). Understanding these processes is key to finding new ways to protect neurons and treat neurodegenerative diseases.

The molecular functions outlined play pivotal roles in the intricate network of neural communication and function, particularly relevant to neurodegenerative diseases.

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Neurotransmitter receptor activity, encompassing various receptor types, is a cornerstone in orchestrating neuronal signalling (Sarapultsev et al., 2023). Dysfunction in these receptors can precipitate disruptions in synaptic transmission, contributing to the pathogenesis of conditions like Alzheimer's and Parkinson's diseases (Lepeta et al., 2016). G protein-coupled receptors (GPCRs), including those responding to amines and serotonin, profoundly affect on mood regulation, cognition, and motor control (Boczek et al., 2021). Alterations in GPCR signalling have been implicated in several neurodegenerative disorders, implicating them as potential therapeutic targets (Azam et al., 2020). Postsynaptic neurotransmitter receptor activity, vital for synaptic plasticity and memory formation, is often compromised in Alzheimer's, exacerbating cognitive decline (Jha et al., 2016). Adrenergic and dopamine receptor activities regulate arousal, attention, and motor function (Arnsten & Pliszka, 2011). Their dysregulation is implicated in various neurological conditions, accentuating the importance of proper functioning (Johnson et al., 2012).

Similarly, histamine receptors influence sleep-wake cycles and cognitive processes, with disturbances in histaminergic signalling contributing to cognitive decline in Alzheimer's (Satpati et al., 2023). The intricate interplay of these receptor activities underscores their significance in neural health and highlights their potential as therapeutic targets for mitigating the progression of neurodegenerative diseases (Adamu et al., 2024). Understanding the mechanisms underlying these receptor activities provides crucial insights into developing novel treatments to combat the devastating effects of these disorders on neuronal function and cognition.

The cellular components identified—such as dendrites, axons, synapses, and cell bodies—are essential parts of neurons that help them communicate. In neurodegenerative diseases like Alzheimer's, Parkinson's, and ALS, these parts get damaged (Wilson III et al., 2023). Dendrites and axons, which extend from the neuron to send and receive signals, can become dysfunctional, disrupting neural communication. Synapses, the contact points between neurons, can also fail, leading to problems in brain function (van Spronsen & Hoogenraad, 2010). The cell body, which maintains the neuron's health, often shows abnormalities, such as toxic protein build-up in Alzheimer's (Camandola & Mattson, 2011). This damage collectively impairs brain function and leads to the symptoms seen in neurodegenerative diseases (Wilson III et al., 2023). Understanding these components helps in finding ways to treat or prevent these conditions.

The KEGG pathway analysis highlights several vital pathways related to brain function and neurodegenerative diseases. Neuroactive ligand-receptor interactions and serotonergic, dopaminergic, and cholinergic synapses are crucial for neurotransmitter signalling in the brain (Yu et al., 2024). Disruptions in these pathways can lead to neurological disorders and diseases like Alzheimer's, which are characterized by impaired neurotransmission (Hampel et al., 2021). The neurotrophin signalling pathway supports neuron survival and function (Chmielarz & Saarma, 2020). Pathways like GnRH signalling and thyroid hormone signalling also influence brain function and neuroendocrine regulation (Oleari et al., 2021).

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Understanding these pathways provides insights into the mechanisms behind neurological diseases and potential therapeutic targets (Decout et al., 2021).

The analysis of disease-gene associations from STRING highlights several conditions related to the nervous system. These include broad categories such as nervous system disease and central nervous system disease, which encompass a variety of disorders affecting the brain and spinal cord. Specific conditions like brain disease, dementia, and neurodegenerative diseases are noted, indicating progressive and often debilitating effects on cognitive and motor functions (Rekatsina et al., 2020). The analysis also identifies nervous system cancers, including malignant glioma and benign neoplasms, which can severely impact neurological health (Salari et al., 2023). Additionally, psychiatric and neurodevelopmental disorders such as ADHD, major depressive disorder, anxiety disorder, obsessive-compulsive disorder, bipolar disorder, and psychotic disorders are included, reflecting the complex interplay between genetics and mental health (Sullivan & Geschwind, 2019). These findings underscore the diverse and multifaceted nature of neurological and neurodegenerative diseases, highlighting the importance of understanding their genetic underpinnings for better diagnosis and treatment (Toader et al., 2023).

In conclusion, the analysis of biological processes (BP), molecular functions (MF), cellular components (CC), KEGG pathways, and diseases provides valuable insights into the intricate mechanisms underlying neurodegenerative diseases. Understanding how neurons respond to stimuli, the functions of neurotransmitter receptors, the organization of cellular structures, the pathways involved in neural signalling, and the diseases that affect the nervous system is essential for developing effective treatments and interventions. By unravelling these complexities, researchers can work towards better therapies to alleviate symptoms, slow disease progression, and ultimately improve the quality of life for individuals affected by neurodegenerative disorders.

CONCLUSION

In conclusion, the analysis underscores the potential of Kawista (Limonia acidissima) as a promising therapeutic agent for neurodegenerative diseases. The integration of network pharmacology approaches revealed intricate molecular mechanisms underlying Kawista's therapeutic effects, emphasizing its modulation of crucial biological processes, neurotransmitter receptors, and signalling pathways implicated in neurodegeneration. Moving forward, continued research into Kawista's therapeutic potential holds promise for the developing of innovative treatments aimed at alleviating symptoms and slowing disease progression, ultimately improving the quality of life for individuals affected by neurodegenerative disorders.

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