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Potential Combination of Dayak onion *Eleutherine palmifolia* L. and Chrysanthemum flower *Chrysanthemum indicum* L. as Anti-aging: Network Pharmacology Approach

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Abstract

Background*: An anti-aging agent is a preparation or product used to inhibit skin aging. Aging occurs because of cell damage caused by free radicals. Therefore, anti-aging agents, which contain antioxidants to inhibit oxidative stress caused by free radicals, are needed. Dayak onion (eleutherine palmifolia (L) Merr.) and chrysanthemum flowers (Chrysanthemum indicum L.) have high antioxidant content, which has the potential to inhibit aging.* ***Objective:*** *To determine the anti-aging potential of dayak onion and chrysanthemum flower compounds* ***Methods:*** *Network pharmacology was performed using GeneCards (https://www.genecards.org) to obtain target genes, Cytoscape v3.10.1 software (https://cytoscape.org), DisGeNET (https://www.disgenet.org), STRING (https://www.string-db.org/), and the Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAY (https://www.genome.jp/kegg/pathway.html).* ***Results:*** *Based on Network Pharmacology, dayak onion and chrysanthemum flowers showed that 14 of the 200 target proteins were involved in biological processes and signaling pathways for premature aging syndrome.* ***Conclusion:*** *The combined compound from dayak onion and chrysanthemum flower has anti-aging activity due to seven bioactive components in the hydroxycinnamic acid group. This compound influences biological processes and longevity by regulating the CAD, SIRT1, and TP53 signaling pathways. Therefore, the combination of dayak onion and chrysanthemum flowers has potential as an anti-aging agent.*

Keywords*: anti-aging, dayak onion, chrysanthemum flower, longevity regulating pathway, network pharmacology*

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INTRODUCTION

An anti-aging agent is a preparation or product used to prevent aging. Aging is a complex biological process characterized by structural changes and skin elasticity, appearance of wrinkles, rough skin, dry skin, and changes in pigmentation (Kumalasari & Prihandiwati, 2019). Aging is caused by environmental factors such as sunlight, air humidity, temperature, cigarette smoke, and air pollution (Nailufa & Najih, 2020). Aging occurs because of cell damage caused by free radicals (Rahmadiani & Hasanah, 2019). The main cause of aging is extrinsic factors due to exposure to UV rays from the sun, which contain free radicals; therefore, Indonesian people are prone to this problem owing to the influence of the tropical climate (Firdayeni & Sari, 2022).

In the human body, oxidation or combustion processes, inflammation, excessive physical activity, and pollution exposure lead to the dynamic formation of free radicals. The overproduction of free radicals can harm macromolecules (lipids, carbohydrates, and nucleic acids) and cells, resulting in aging and degenerative illnesses (Zhang et al., 2020). Enzymatic and non-enzymatic antioxidants protect the body against free radical damage by removing excess ROS and preventing aging. Thus, anti-aging products contain antioxidants that inhibit the oxidative stress caused by free radicals (Kumalasari & Prihandiwati, 2019).

Dayak onion (eleutherine palmifolia (L) Merr.) is a typical Central Kalimantan plant originating from America, containing secondary metabolite compounds of the flavonoid group, naphthoquinone group, and their derivatives (eleutherin, eleutherol, eleutherinol, eleutherionin, eleuthoside B, and eleuthoside A), as well as the polyphenol group (oxyresveratrol) (Muti'ah et al., 2020). According to Pramiastuti et al. (2021), dayak onions have secondary metabolites with IC50 values for flavonoids, alkaloids, tannins, saponins, phenolics, and steroids or triterpenoids with antioxidant or anti-free radical properties. According to Novaryatiin et al. (2019), dayak onions contain alkaloids, flavonoids, quinones, polyphenols, saponins, steroids, monoterpenoids and tannins. The flavonoid group in dayak onion has the ability to transform to produce antioxidant activity that inhibits free radicals (Mokoginta et al., 2020). The useful part and the part used in this research is dayak onion bulbs.

Chrysanthemum flower (*Chrysanthemum indicum* L.) is a shrub or semi-shrub and sub-tropical plant originating from Japan and North China which is very popular among people because it has aesthetic value and has a variety of colors, and is used as an ingredient in traditional medicine (Sembiring et al., 2021). Chrysanthemum flower are generally only used as cut flowers, even though these flowers contain high levels of antioxidants including flavonoids, tannins, terpenoids, alkaloids, steroids and saponins (Puspita et al., 2023). Chrysanthemum flowers have antioxidant, anti-inflammatory, antineoplastic, antidiabetic, antibacterial, and lipid-lowering properties, and contain flavonoids in the form of quercitrin, myricetin, and luteolin 7-glucoside (Hartanto et al., 2021). According to Marlina and Widiastuti (2021), the main secondary metabolite in chrysanthemum flowers is pyrethrin (12.66 %). Chrysanthemum flowers have the potential for anti-aging because they contain active components, such as essential oils, terpenoids, flavonoids, and phenolic acids, as well as being a source of quercitrin and myricetin. The major flavonoid components included 7-O-β-D-gulocoside and linarin such as phenolic acids from chlorogenic acid, 3,5-di-O-Caffeoylquinic acid, 3,4-di-O-caffeoylquinic acid, and 4, 5-di-O-caffeoylquinic (Wanita, 2022).

Dayak onions and chrysanthemums can potentially be used as anti-aging agents based on their antioxidant content. This is because aging can be overcome by administering natural antioxidant compounds. Flavonoids can prevent the occurrence of Reactive Oxygen Species (ROS), protect the skin from damage, and inhibit specific skin aging enzymes (Kumalasari & Prihandiwati, 2019). Processing dayak onion and chrysanthemum flowers, considering their use as anti-aging agents, has never been studied. This development will have an impact on two things, namely, the cultivation and development of dayak onion and chrysanthemum flowers, as well as anti-aging.

MATERIALS AND METHODS

Tools

The ingredients used in this research for network pharmacology tests are GeneCards (https://www.genecards.org) to obtain target gens, Cytoscape v3.10.1 software (https://cytoscape.org), DisGeNET (https://www.disgenet.org), STRING (https://www.string-db.org/), and the Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAY (https://www.genome.jp/kegg/pathway.html).

Method

Network pharmacology test

Network pharmacology uses an integrated network of biological systems and computer analysis technology to determine the active components and mechanisms of an active ingredient with target proteins (Tjandrawinata et al., 2022). This method combines network biology with polypharmacology, based on the effectiveness of highly selective compound target proteins, capable of identifying compounds and disease targets from large amounts of data and understanding their mechanisms and pathways of activity including exploring the basic pharmacological effects of a compound on disease and its mechanisms (Zhou et al., 2020). Network pharmacology was used to investigate the molecular mechanisms of dayak onion and chrysanthemum flowers, which play an important role in inhibiting free radicals that cause aging. The computational approach in this method can accommodate large and fast data, as well as promising results for the study of active ingredients, such as dayak onion and chrysanthemum flower (Syahrir et al., 2016).

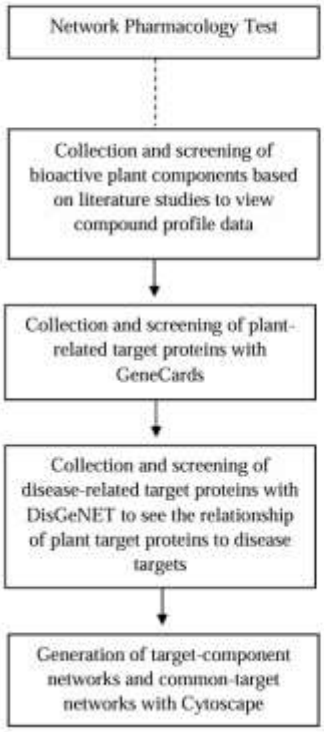


Figure 1. Network pharmacology test flow

Collection and screening of bioactive components of dayak onion and chrysanthemum flower

The bioactive compound components of dayak onion and chrysanthemum flower were obtained based on the results of a literature study from other scientific research indexed by Google Scholar with the keywords "*Chrysanthemum indicum* compound" and "*Eleutherine palmifolia* compound." The components selected were those with high levels and dominated based on comparative literature studies.

Collection and screening of target proteins related to dayak onion and chrysanthemum flower

Target proteins and genes related to anti-aging were obtained from GeneCards (Permatasari et al., 2021). GeneCards is a searchable integrative database that provides comprehensive, easy-to-use information on all annotated and predicted human genes. The knowledge base automatically integrates data, including genomic, transcriptomic, proteomic, genetic, clinical, and functional information. The targets that yield results from GeneCards are restricted to those with a relevance value of ≥10.00, as this value is deemed to satisfy the database requirements (Tjandrawinata et al., 2022). Target protein association data are then associated with diseases from the DisGeNET database, which contains data on genes and variants associated with human diseases.

Collection and screening of disease-related target proteins and creation of target networks

Next, we explored the target genes associated with anti-aging using DisGeNET. DisGeNET is a method for collecting disease target data by searching a database that contains information about the connections between proteins and disease targets (Rosyadah et al., 2017). The next step is to create a target network related to dayak onion and chrysanthemum flowers that are collected into a target-component network, which is then visualized through a similarity network using Cytoscape v3.10.1 (Qomariasih et al., 2016). The target proteins and bioactive components of dayak onion and chrysanthemum flower are represented as “nodes” and the interactions between the two proteins as “edges.” The more important the proteins that are the targets of a component, the more that component can be designated as an important component (Tjandrawinata et al., 2022).

Creation of a protein-protein interaction network (PPI network) and enrichment analysis

Using the (STRING) platform, Gene targets at the intersection of the active ingredient and disease were selected for further analysis using the STRING platform. PPI network analysis utilized gene ontology (GO) functional annotations, enrichment of protein pathways by the Kyoto Encyclopedia of Genes and Genomes (KEGG), and their functions in signal transduction. PPI networks were constructed using common target proteins with a minimum interaction score of 0.400 (Tjandrawinata et al., 2022).

RESULTS AND DISCUSSION

Collection and screening of bioactive components of Dayak onion and Chrysanthemum flower

Based on the results of a literature study using the Google Scholar search engine with the keywords "Chrysanthemum indicum compound" and "Eleutherine palmifolia compound" the following results were obtained (Tables 1 and 2).

Collection and screening of target proteins related to dayak onion and chrysanthemum flower

Based on the collection and screening of target proteins from the GeneCards database with a relevance value ≥10.00, 260 target proteins from various types of compounds were obtained, as shown in Table 3.

Table 1. Bioactive components of dayak onion

Compound Name	Molecular Type	Ppubchem CID	References
Naphthoquinone Naphthalene	Quinones	931	(Kamarudin et al., 2021; Muti'ah et al., 2020; Narko et al., 2017)
Oxyresveratrol	Polyphenols	5281717	(Muti'ah et al., 2020; Qureshi & Javed, 2022; Wahdaningsih et al., 2023) (
Isoliquiritegenin	Flavonoids	135031285	(Muti'ah et al., 2020)
Sitosterol	Steroids	3084097	(Saputra et al., 2016)

Table 2. Bioactive components of chrysanthemum flower

Compound Name	Molecular Type	Ppubchem CID	References
Quercitrin; Myricetin; luteolin 7-glucoside; Apigenin; Luteolin; Kaempferol; Diosmetin	Flavonoids	5280343 5281672 5280637 5280443 5280445 5280863 5281612	Chen et al., 2021; Hartanto et al., 2021; Marlina & Widiastuti, 2021; Wanita, 2022; Click or tap here to enter text. Wang et al., 2019; Yuan et al., 2020; Zhou et al., 2023)
1,3-dicaffeoylquinic acid; 3,4-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; 3,5-dicaffeoylquinic acid; 1,4-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid; Chlorogenic acid; Caffeic acid	Hydroxycinnamic acids	6474640 6474309 122685 13604688 12358846 5281780 1794427 689043	(Chen et al., 2021; Lin & Harnly, 2010; Jiang et al., 2022; Ma & Wako, 2017; Zhou et al., 2023)
β-carotene, α-carotene	Carotenoids	5280489, 6419725	(Chen et al., 2021)

Table 3. Target protein screening results

Compound type	Number of Gene Targets	Gifts Range	Relevance Range
Sitosterol	3	44-49	14-23
Naphthoquinone	1	52	11
1,3-dicaffeoylquinic acid	4	13-25	17-29
3,4-dicaffeoylquinic acid	4	14-55	10-22
1,5-dicaffeoylquinic acid	4	51-57	18-26
3,5-dicaffeoylquinic acid	3	13-57	19-29
1,4-dicaffeoylquinic acid	2	55	17-25
4,5-dicaffeoylquinic acid	4	55-57	12-23
Chlorogenic acid	59	13-57	10-40
Caffeic acid	175	11-59	10-108
Total	**260**		

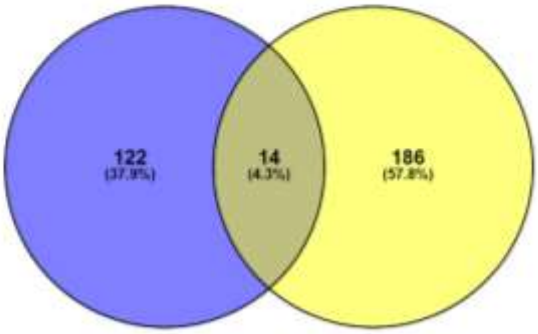


Figure 2. Venn diagram of 200 target proteins of dayak onion and chrysanthemum flower against premature aging syndrome

Collection and screening of disease-related target proteins and creation of target networks

Of the 260 target proteins, there are 60 identical target proteins and 200 different target proteins that are associated with 14 specific target proteins related to anti-aging (Premature Aging Syndrome) through DisGeNET. This network pharmacology study revealed 14 target proteins related to anti-aging, which are the main targets where these proteins lock and interact with each other.

Based on the Venn diagram (Figure 2), there were 14 genes whose interactions were anti-aging. Yellow represents 200 target genes from dayak onion and chrysanthemum flowers, while blue represents 136 target genes for premature aging syndrome. A number of target genes that have anti-aging interactions include APP (*Amyloid-beta A4 protein*), TP53 (*Cellular tumor antigen p53*), SIRT1 (Sirtuin-1), SOD1 (*Superoxide dismutase*), VDR (*Vitamin D3 receptors*), CDKN1A (*Cyclin-dependent kinase inhibitor 1*), BCL2 (B2 cell lymphoma), CAT (Catalase), MAPK1 (*Mitogen-activated protein kinase 1*), NFE2L2 (*Nuclear factor erythroid 2-related factor 2*), POLG (*polymerase subunit gamma-1*), MMP9 (*Matrix metalloproteinase-9*), GUSB (*Beta-glucuronidase*), IL1B (*Interleukin-1 beta*). Next, the target network obtained from the Cytoscape v3.10.1 visualization results obtained protein-target protein interactions, as shown in Figure 3.

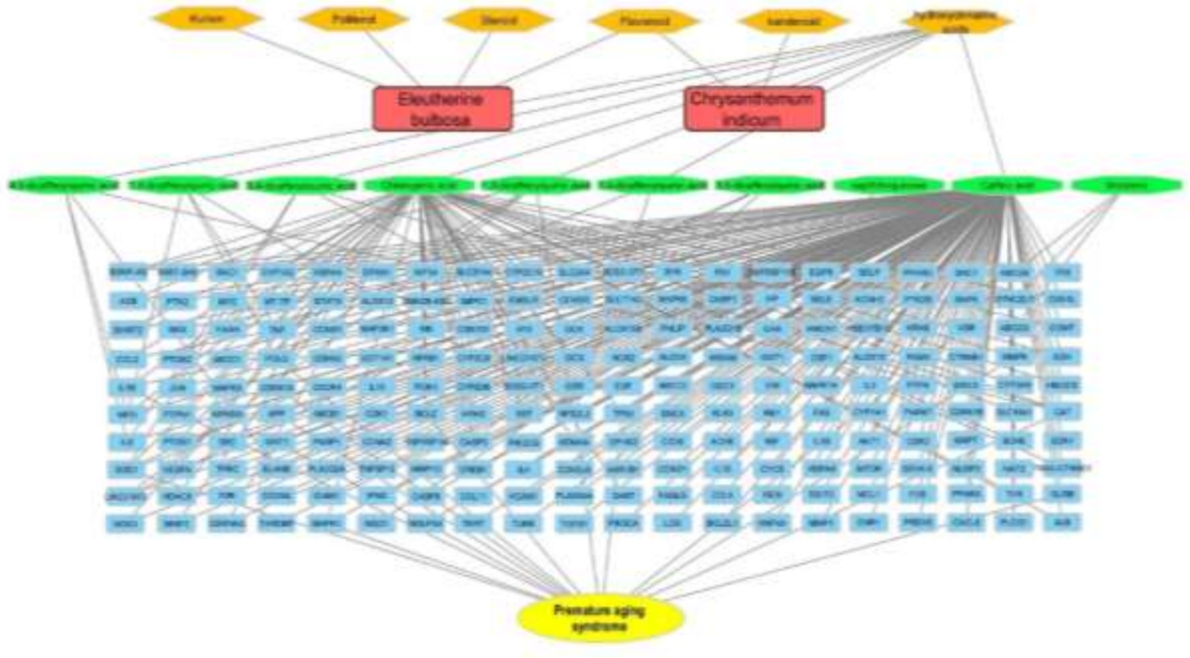
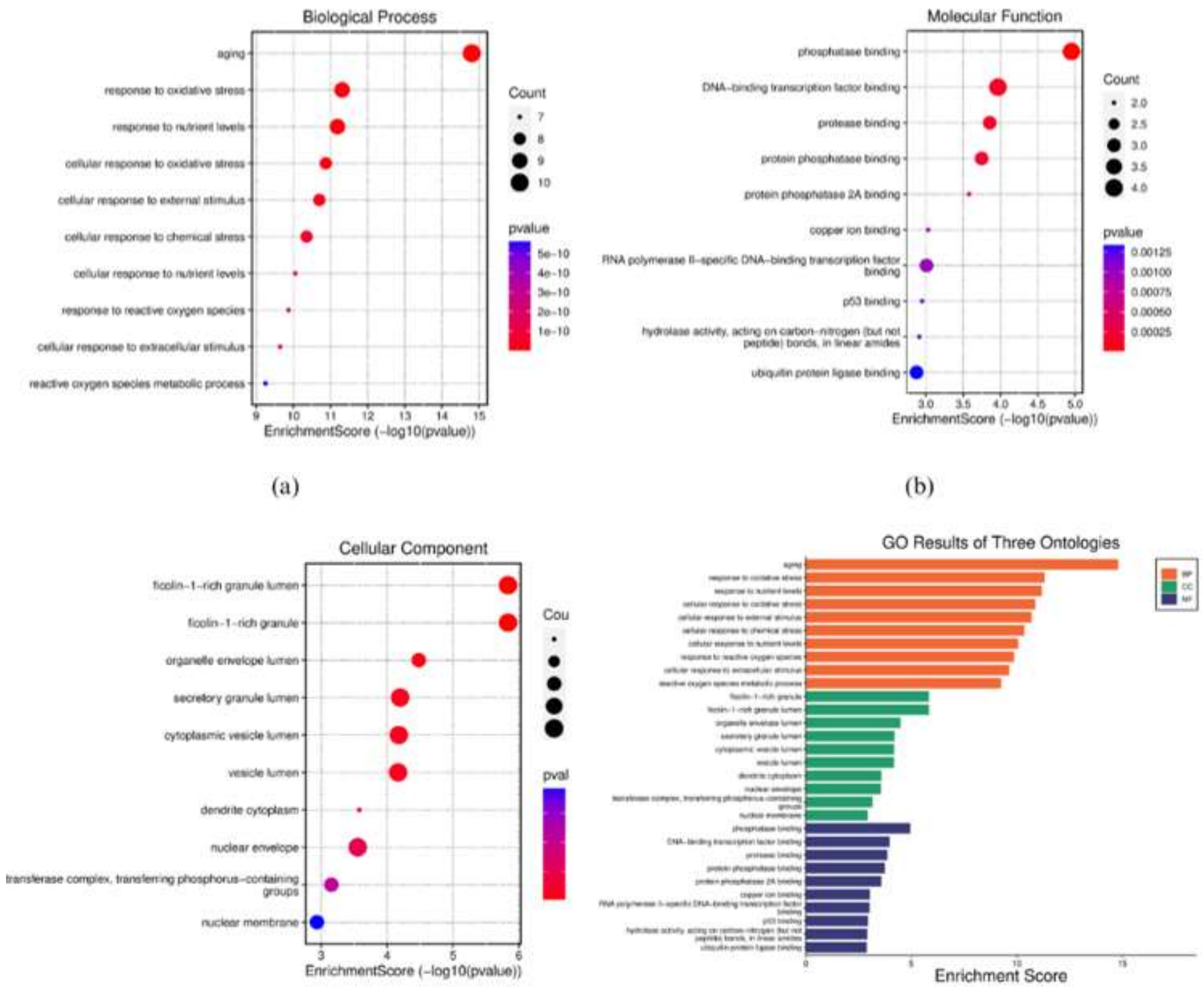


Figure 3. Visual network of dayak onion and chrysanthemum flower (Red: plant name, Orange: compound molecules, Green: Bioactive components, Yellow: Disease, Blue: Target protein)



(a) (b)

(c) (d)

Figure 4. Interaction network of 14 core proteins from STRING database (14 nodes, 48 edges, PPI enrichment p-value: 4.68e-12); (a) 14 target genes interact as aging; (b) 4 target genes involved in anti-aging biological processes

In the visual target network (Figure 2), there were 14 target proteins (APP, TP53, SIRT1, SOD1, VDR, CDKN1A, BCL2, CAT, MAPK1, NFE2L2, POLG, MMP9, GUSB, and IL1B) from seven bioactive components that had target proteins related to anti-aging, namely chlorogenic acid, caffeic acid, 3,4-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, 1,3-dicaffeoylquinic acid, 1,5-dicaffeoylquinic acid, and 1,4-dicaffeoylquinic acid. These active components are some of the important molecules with anti-aging activities, namely hydroxycinnamic acids. According to Cizmarova et al. (2020), hydroxycinnamic acids can influence aging by increasing skin elasticity and providing positive anti-wrinkle effects owing to natural bioactive compounds. Additionally, its antioxidant activity increases collagen production and prevents premature aging. The antimicrobial activity of This compound has also been proven to have anti-wrinkle activity in vivo and is effective against skin problems. Considering that most of the bioactive components belong to caffeic acid, Bastianini et al. (2018) reported that acaffeic acid is a very promising hybrid owing to its higher bioavailability and prolonged antioxidant activity in the skin.

Creation of a protein-protein interaction network (PPI Network) and enrichment analysis

Protein-protein interactions (PPI) are physical or functional interactions between two or more proteins that play key roles in various cellular processes. The results obtained in this study highlight the relationship between various types of proteins in dayak onion and chrysanthemum flowers, which have an anti-aging role. Dayak onion and chrysanthemum flowers contain multiple components that act on multiple targets through various mechanisms of action. Through this network pharmacology study, the mechanism of action of dayak onion and chrysanthemum flowers can be described at the molecular level more comprehensively in terms of signaling pathways.

Based on the enrichment analysis of the mechanism of action of dayak onion and chrysanthemum flower as potential anti-aging agents, the results of KEGG analysis identified the target genes that were most associated with the data: TP53 (*cellular tumor antigen p53*), SIRT1 (Sirtuin-1), SOD1(*superoxide dismutase*), and CAT (catalase).

The results of gene ontology analysis showed that the compounds contained in dayak onion and chrysanthemum flower are mainly chlorogenic acid, caffeic acid, 3,4-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, 1,3-dicaffeoylquinic acid, 1,5-dicaffeoylquinic acid, and 1,4-dicaffeoylquinic acid, which are involved in biological processes, molecular functions, and cellular components. In the bubble-shaped enrichment picture, it was found that there are 10 biological processes that have high potential, where aging has the highest significance value, involving as many as 10 genes. This was followed by oxidative stress, nutrient levels, etc., involving genes in the range 7-9 as shown in Figure 4A. In addition, these compounds also affect molecular functions, where the 10 molecular functions with the highest potential were shown by phosphatase binding involving four genes. Next, DNA-binding transcription factor binding, protease binding, and so on, with a range of genes involved from 2-3.5 as shown in Figure 4B. Meanwhile, the highest potential cellular components were ficolin-1-rich granule lumen and rich granules, as shown in Figure 4C. All enrichment scores for biological processes, cellular components, and molecular functions can be seen in the 4D image bar diagram with interpretation of the values presented.

This study showed that dayak onion and chrysanthemum flowers affect the biological processes and signaling pathways of type 2 DM toward TP53 (*cellular tumor antigen p53*) and SIRT1 (Sirtuin-1).

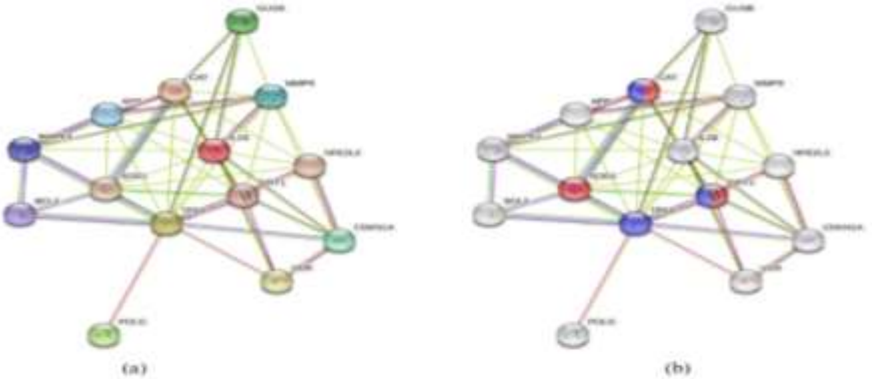

(a) (b)

Figure 5. KEGG Gene Ontology and Pathway Enrichment Analysis; (a) Enrichment bubble diagram of 10 biological processes with high potential; (b) Enrichment bubble diagram of 10 molecular functions with high potential; (c) Enrichment bubble diagram of 10 cellular components with high potential; (d) GO bar diagram of enrichment for biological processes, molecular functions, and cellular components

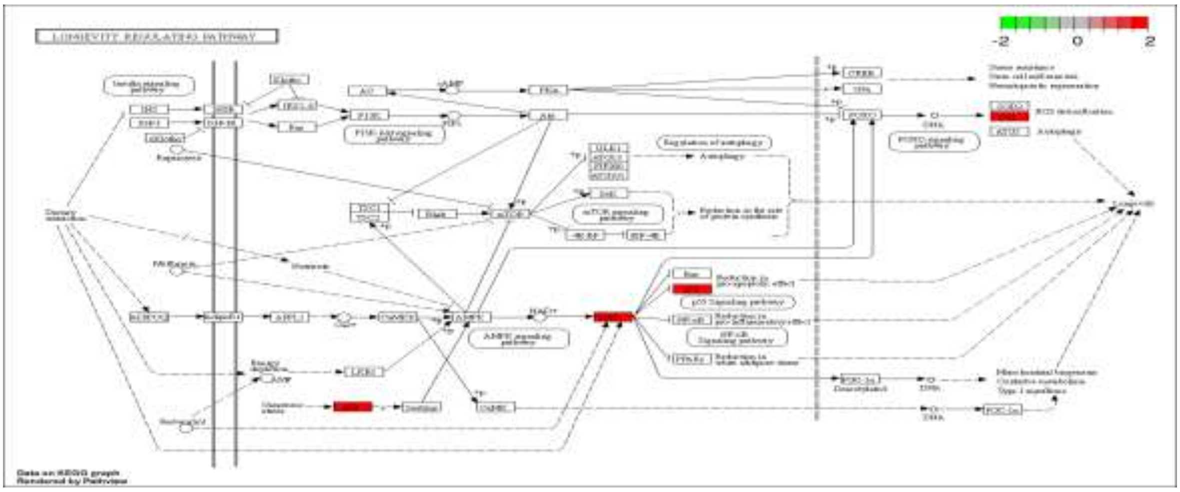


Figure 6. Signaling pathway involving three potential target genes (red marks) in anti-aging activity

Table 4. Results of the KEGG gene interaction analysis

Pathways	Description	Count in network	Strength	False Discovery Rate	Genes
Hsa04213	Longevity regulating pathway-multiple species	3 of 61	1.84	0.00021	CAT, SIRT1, SOD1
hsa04211	Longevity regulating pathway	7 of 46	1.6	8.70e-09	CAT, SIRT1, TP53

TP53 is involved in cell cycle regulation as a trans-activator that negatively regulates cell division by directing several essential genes. It also functions as a tumor suppressor in many different types of cancers and can induce growth arrest or apoptosis, depending on the physiological state and type of cell. TP53 protein is often called the guardian of the genome because it is an important factor in maintaining genome stability, which induces cell senescence and apoptosis if genome instability occurs, which induces the aging process (Siswanto & Kartiko, 2017). In this case, the TP53 process is anti-aging and prevents or repairs damage at the genomic level.

SIRT1 is a master regulator associated with aging that helps coordinate multiple distinct cellular processes, including the cell cycle, response to DNA damage, metabolism, apoptosis, and autophagy. It also directly connects transcriptional regulation with intracellular energy, as well as modulating chromatin function through histone deacetylation, and can induce changes in histone and DNA methylation, leading to transcriptional repression, which is involved in decisions regarding cellular senescence or apoptosis. In SIRT1, pleiotropic activity is an important marker of cellular aging, as well as in several diseases such as cardiovascular and neurodegenerative diseases, diabetes, and cancer. Generally, with increasing age, SIRT1 levels decrease in the aging liver, whereas there is a simultaneous increase in the accumulation of DNA damage (Grabowska et al., 2017). Vascular aging is accelerated in the liver, heart, kidney, brain, and lung by a decrease in SIRT1 expression in endothelial cells (EC), vascular smooth muscle cells (VSMC), and macrophages. SIRT1 contributes to the inhibition of aging of nucleus pulposus cells, promotion of cell division, inhibition of apoptosis, and inhibition of UV-induced fibroblast aging, as well plays a role in crucial cellular activities including response to stress, metabolism and longevity (cell senesce) (Chen et al., 2020).

CAT protects cells from the harmful effects of hydrogen peroxide and stimulates the proliferation of several cell types, including T cells, B cells, melanoma, mastocytoma, myeloid leukemia, and normal and altered fibroblast cells. CAT significantly contributes to the antioxidant defense of cells by dissolving hydrogen peroxide in oxygen and water. According to its pleiotropic significance, CAT is linked to a reduction or impairment in age-related diseases with a shorter lifetime (Dutta et al., 2022).

CONCLUSION

Based on network pharmacology, dayak onion and chrysanthemum flowers showed that 14 of the 200 target proteins were involved in the biological processes and signaling pathways of premature aging syndrome with target locking and interaction. The 14 target proteins are compound molecules in dayak onion and chrysanthemum flowers, which are included in the seven bioactive components of the hydroxycinnamic acid group. These compounds affect biological processes and signaling pathways of longevity regulators for TP53, SIRT1, and CAT through mechanisms already explained. Therefore, the combination of dayak onion and chrysanthemum flowers has the potential to have anti-aging effects.

AUTHOR CONTRIBUTIONS

Conceptualization, R.M., F., S.E.S.N.; Methodology, R.M., F., S.E.S.N.; Software, R.M., F., S.E.S.N.; Validation, R.M.; Formal Analysis, S.E.S.N.; Investigation, F.; Resources, S.E.S.N.; Data Curration; S.E.S.N.; Writing - Original Draft, S.E.S.N.; Writing - Review & Editing, F.; Visualization, F.; Supervision, R.M.; Project Administration, R.M.; Funding Acquisition, R.M.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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