ARTICLE

Multiple system biology approaches reveals the role of the hsa-miR-21 in increasing risk of neurological disorders in patients suffering from hypertension

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Hypertension is a prevalent disease that substantially elevates the risk of neurological disorders such as dementia, stroke and Parkinson's disease. MicroRNAs (miRNAs) play a critical role in the regulation of gene expression related to brain function and disorders. Understanding the involvement of miRNAs in these conditions could provide new insights into potential therapeutic targets. The main objective of this study is to target and investigate microRNAs (miRNAs) associated with neurological disorders in patients suffering from hypertension. The genes involved in hypertension were identified from various databases including GeneCard, MalaCard, DisGeNet, OMIM & GEO2R. The key gene for hypertension was identified using a systems biology approach. Also, potent phytochemical for hypertension was determined by computer-aided drug-designing approach. Functional miRNAs were determined for the key target gene using miRNet analytics platform by hypergeometric tests. Further, the gene-miRNA interaction was determined and enrichment analysis was done. RPS27A was identified as a key target gene for hypertension. Naringenin showed effective molecular interaction with RPS27A with a binding energy score (−6.28). Further, a list of miRNAs which were targeting brain disorders was determined from miRNet. A gene-miRNA network was constructed using the PSRR tool for Parkinson's Disease, Autism Spectrum Disorder, Acute Cerebral Infarction, ACTH-Secreting Pituitary Adenoma, & Ependymoma. Further, miRNA 21 & miRNA 16 were found to be associated with four of the neurological disorders. The study identifies specific miRNAs that may serve as potential biomarkers for brain disorders in hypertensive patients. Targeting these miRNAs could open new avenues for therapeutic strategies aimed at mitigating neurological damage in this patient population.

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INTRODUCTION

Hypertension is one of the major health conditions globally, whose exact molecular cause is still not known [1]. It is certainly elucidated by a continual increase in arterial pressure. Systolic blood pressure (SBP) of 130 mm Hg or higher and/or diastolic blood pressure (DBP) of 80 mm Hg or higher are present-day parameters for hypertension (HTN) [2]. The most prevalent global cause of life expectancy adjusted for disability is hypertension, and high blood pressure (BP) is the main risk factor for cardiovascular disease (CVD) [3, 4]. Pharmacological treatment works quite well at decreasing blood pressure and averting the consequences of CVD [5] for majority of the patients [6].

Over 25% of individuals suffer with hypertension. Subclinical cerebrovascular abnormalities [7], dementia, and stroke are examples where hypertension-induced organ damage first targets the brain [8]. Neurological symptoms are likewise prevalent among hypertensive conditions. An inability to increase cerebral blood flow at low blood pressure, endothelial dysfunction, luminal constriction, cerebral vascular atherosclerosis, and reduced arterial relaxation are all associated with persistent hypertension [9]. The primary and secondary prevention of stroke can be achieved with great success using antihypertensive medication [10]. In individuals with hypertension, antihypertensive drug therapy is quite successful in primary stroke prevention [11, 12]. Studies has shown that hypertension is a significant risk factor for cognitive decline and neurodegenerative brain disorders in the future [13].

Hypertension is a circulatory condition and is very harmful to one's health and longevity [14]. It impairs the operation of vital organs and is often associated with a number of secondary conditions that require long-term medication therapy [15]. According to estimates that show an annual increase in the number of patients with the condition [16, 17]. The most important complications as shown in Fig. 1, that have been linked to the development of cardiac failure [18], kidney dysfunction [19], myocardial infarction, and stroke [2, 20] and various secondary diseases which severely affects the lives of patients [21].

Recent research has demonstrated the role that miRNAs play in the onset and course of essential hypertension [22, 23], a prevalent kind of high blood pressure that impacts millions of people globally. The many and varied biological pathways via which miRNAs control hypertension [24]. Cell division, cell death, proliferation, cancer, and stress response are just a few of the many biological processes which may led to hypertension [25–28]. For instance, it has been shown that some miRNAs control the expression of genes connected to the renin-angiotensin-aldosterone system (RAAS) [29–31], which is essential for

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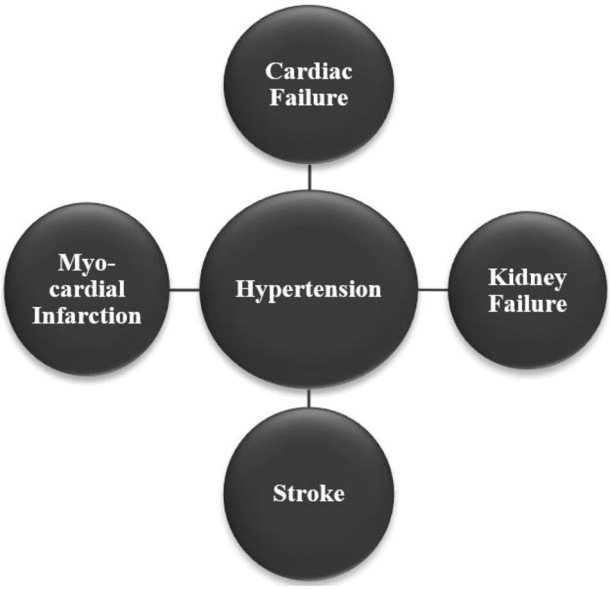


Fig. 1 Major diseases associated with hypertension. This schematic diagram illustrates the range of critical diseases that are impacted by hypertension, including cardiac failure (top), myocardial infarction (left), kidney failure (right), and stroke (bottom). Hypertension serves as the central factor influencing each of these conditions.

controlling blood pressure [32]. Many new discoveries about essential hypertension have recently come to light, and these offer crucial theoretical support for the advancement [33] of essential hypertension knowledge and care.

Systems biology has applications in almost every field of medicine, including hypertension and the vascular problems that are underlying [34]. Network pharmacology (NP) uses computational techniques to methodically catalogue a drug molecule's molecular connections in addition to facilitating the recognition of various pharmacological effects and interactions with numerous targets [35, 36]. The next generation of promiscuous medications might be effectively designed by integrating systems biology with NP breakthroughs [37–39].

The current approach for this study involves integrating systems biology and network pharmacology approaches. Key target gene for hypertension was identified. Additionally, a natural phytochemical with possible anti-hypertensive properties was identified using various in silico techniques. Ultimately, new discoveries in the field of miRNA research have shed light on the fundamental causes of hypertension, despite the fact that it is a complicated multifactorial disease.

METHODOLOGY

The graphical abstract illustrates the integrated computational approach employed in this study. Hypertension-associated genes were identified and analyzed through protein-protein interaction (PPI) network construction to determine key targets. The key gene, RPS27A, was structurally modelled and subjected to molecular docking studies with various phytochemicals, identifying naringenin as the most promising candidate. Concurrently, functional miRNAs targeting RPS27A were identified, and gene-miRNA interaction networks were constructed. Finally, the regulatory effect of naringenin on brain-associated miRNAs was evaluated, highlighting its potential therapeutic role in mitigating neurological complications associated with hypertension as shown in Fig. 2.

Data mining for gene identification

Numerous gene databases and studies were used to identify the genes associated with hypertension. Databases from where genes were taken were MalaCard [40], GeneCard [41], DisGeNet [42], OMIM [43] and differentially expressed genes from the GEO2R analyzer of GEO datasets [44]. All of them were comprehensive collections of validated diseases compiled from various data sources. All the genes were compiled, and duplicates were eliminated for further network construction.

Protein-protein interaction network for key target identification

Network biology was used to identify the key target gene. Using the Cytoscape STRING plugin, a network of all the distinct genes coding for hypertension was constructed having a confidence score of 0.98. The network of the top 20 hub genes was constructed by using Cytohubba plugin of Cytoscape [45]. Twelve Cytohubba parameters were used to investigate the interaction. Additionally, a manual analysis of the hub gene network was conducted to identify the primary target gene for hypertension.

Protein structure prediction, validation & molecular docking studies

The protein sequence of RPS27A receptor (*Homo sapiens*) having accession number P62979 was retrieved from UniProt database [46] retrieved in FASTA format. The three-dimensional structure of RPS27A receptor was predicted using online modelling server Swiss Model [47]. In addition, a PDB file containing the three-dimensional structure was retrieved. Further, the predicted structure was validated using Procheck [48] and ERRAT plot [49] of SAVE server. The Ramachandran plot [50] was used to evaluate the position of amino acid residues in the allowed and disallowed region.

By employing literature study findings, a curated list of phytochemicals with anti-hypertensive properties was compiled. Phytocompounds were identified based on their natural source. Also, the canonical smiles of each one were retrieved from PubChem [51]. Further, the phytochemicals following Lipinski's rule of five were identified using ADMET Lab 3.0 [52].

A molecular docking study was performed for all the anti-hypertensive phytochemicals retrieved with predicted model of RPS27A receptor using Seam Dock [53] online tool for predicting the best binding energy score. Seam Dock performed both the molecular interaction of the receptor (RPS27A) with ligands (phytochemicals) and the visualisation of that interaction.

Gene-miRNA interaction & enrichment analysis

The functional miRNAs that target the key gene related to brain tissue were identified from miRNet platform. Also, miRNet [54] provides insights into the biological pathways associated with RPS27A. Further, the hypergeometric test was done to identify the diseases associated with miRNAs by network construction. The network had a degree of 26 and a betweenness of 325. Later, enrichment analysis was done.

Effect analysis of phytocompound on miRNA expression

The effect of the phytocompound naringenin was seen on the miRNAs through the PSRR (Prediction of SM-miRNA Regulation pairs by random forest) tool. PSRR is an efficient web server through which small molecule expression on miRNA regulation can be predicted using a random forest machine learning algorithm [55]. This shows whether the phytocompound has a positive or negative regulation on the expression of the miRNAs.

RESULTS

Data mining for gene identification

Among the gene databases listed above, a total of 17302 genes were found. RNA-Seq data analysis identified 4411 genes involved in hypertension. The criteria set for the identification of differentially expressed genes in patient samples was p-adjusted value less than 0.05 and log 2-fold change greater than 0 (for upregulated genes)

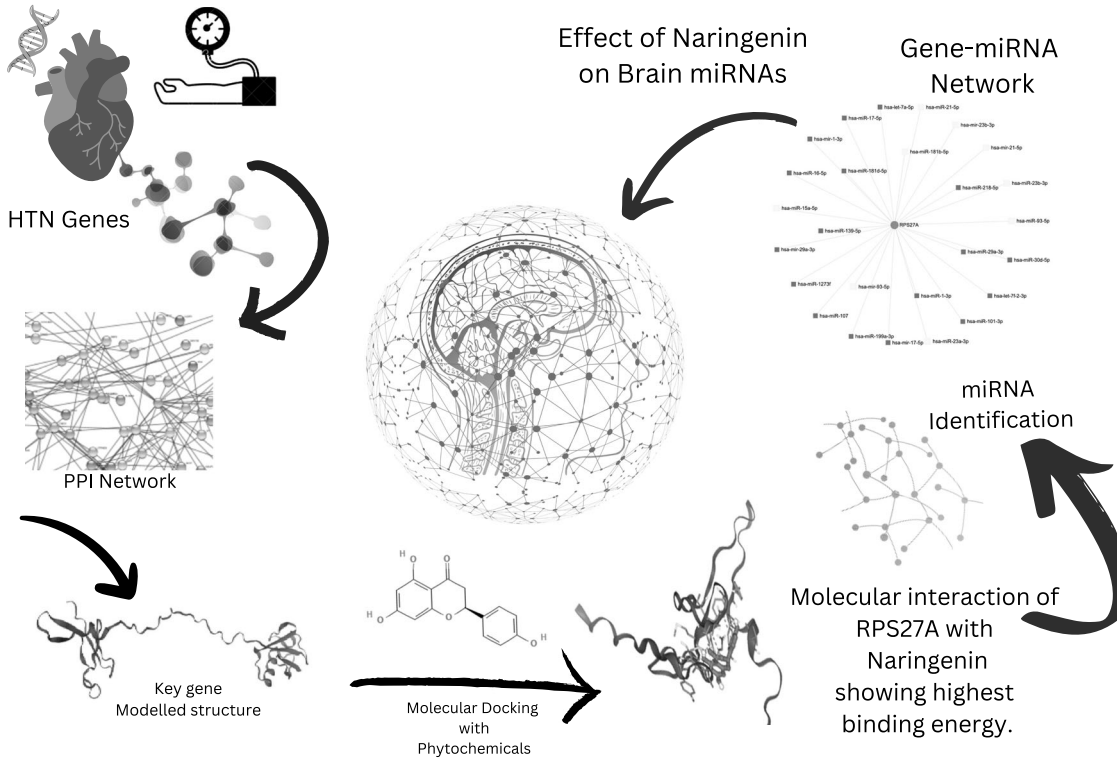


Fig. 2 Schematic workflow of the methodology used to explore the effect of Naringenin on brain miRNAs in hypertension. The flow diagram outlines the sequential steps followed in the study: identification of hypertension (HTN)-associated genes, construction of a protein–protein interaction (PPI) network, modeling of key gene structures, molecular docking with phytochemicals, and analysis of molecular interactions. The process further includes miRNA identification, construction of gene–miRNA interaction networks, and assessment of Naringenin's regulatory effect on brain-related miRNAs, with RPS27A showing the strongest binding affinity.

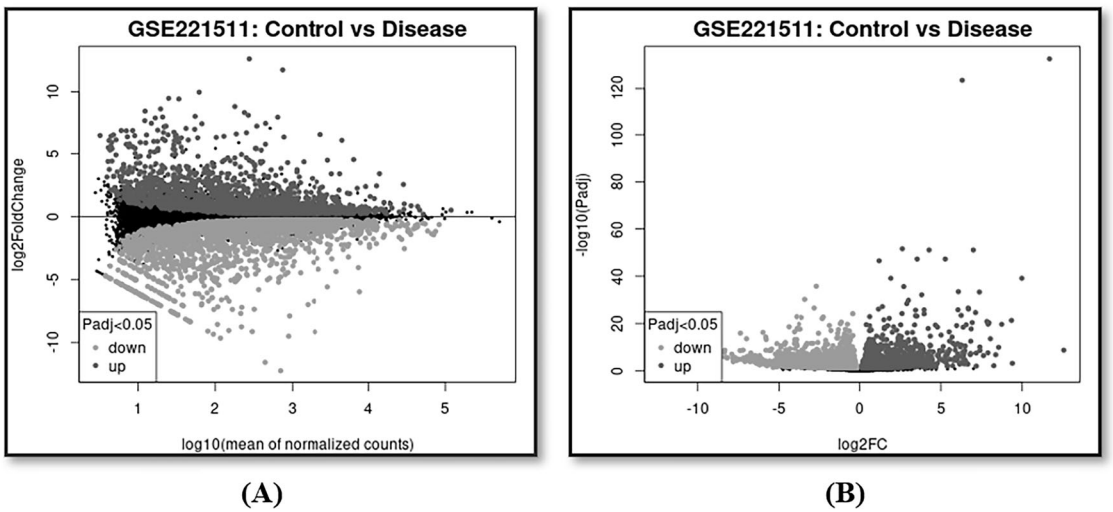


Fig. 3 MA plot and Volcano plot of differentially expressed genes (DEGs) identified from GEO2R. A MA plot displaying the relationship between the log-fold change and average expression levels of DEGs. **B** Volcano plot showing the significance (p-value) vs. magnitude (log-fold change) of DEGs. The red and green dots represent upregulated and downregulated genes, respectively, while gray dots indicate non-significant genes.

and less than 0 (for downregulated genes). DEGs were also identified from GEO2R which can be seen in MA and Volcano plots as shown in Fig. 3. Apart from RNA-Seq data analysis, 343 genes were obtained from MalaCard, 11,822 genes from GeneCard, 156 genes from DisGeNet, and 570 genes from the OMIM database of NCBI (Table 1). 2746 duplicated genes were removed from the list of genes. A total of 14556 specific genes were found.

Protein-protein interaction network for key target identification

The protein–protein interaction of hypertension at a 0.98 confidence score displayed a network of 10,694 nodes and 22,077 edges after eliminating single tones and functional enrichment of the constructed network. The network was further subjected to CytoHubba plugin of Cytoscape for the identification

of 20 hub genes involved in the network on the basis of 12 important parameters. RPS27A was identified as the key target gene. The gene was common in 7 out of 12 parameters. Networks for the same is shown below in Fig. 4. Also, through functional enrichment of these networks it has been observed that RPS27A gene along with several genes like RPS11, RPS3, RPS2, RPS13, RPL23A, RPL11, RPS3A and others are involved in reactome pathways like peptide chain elongation, viral mRNA translation, GTP hydrolysis and joining of 60S ribosomal unit, rRNA processing in the nucleus and cytosol, eukaryotic translation termination etc.

Table 1. Sum of all the genes found using various databases.

Database Name	Number of Genes
MalaCard	343
GeneCard	11822
DisGeNet	156
OMIM	570
GEO Datasets	4411
Total	17302

Protein structure prediction, validation & molecular docking studies

Using the Swiss Model server, the protein's tertiary structure was predicted. The three-dimensional structure of the RPS27A protein is shown in Fig. 5. For the modelled structure, A quality factor of 100 on the ERRAT plot suggests non-bonded contact with distinct atoms in the projected structure, while a 93.5% residue percentage in the favourable area on the Ramachandran plot indicates strong structural stability and dependability.

A total of 20 anti-hypertensive phytochemicals were identified from various literature studies, which followed the five rules of Lipinski. Phytocompound name list is depicted in Table 2. After performing molecular docking with the receptor RPS27A for each of the 20 phytochemicals, the binding energy and amino acid residues detected are displayed in Table 2. Out of all the 20 anti-hypertensive phytochemicals, naringenin had shown the best binding energy score of −6.28 kcal/mol (Fig. 6).

Gene-miRNA interaction & enrichment analysis

A total of 26 functional miRNAs were identified for the nervous tissue from miRNet. Also, there was an association of these miRNAs with five of the neurological disease pathways as shown in Table 3. An enrichment analysis of the network of the RPS27A with the miRNAs was constructed as depicted in Table 4. Further,

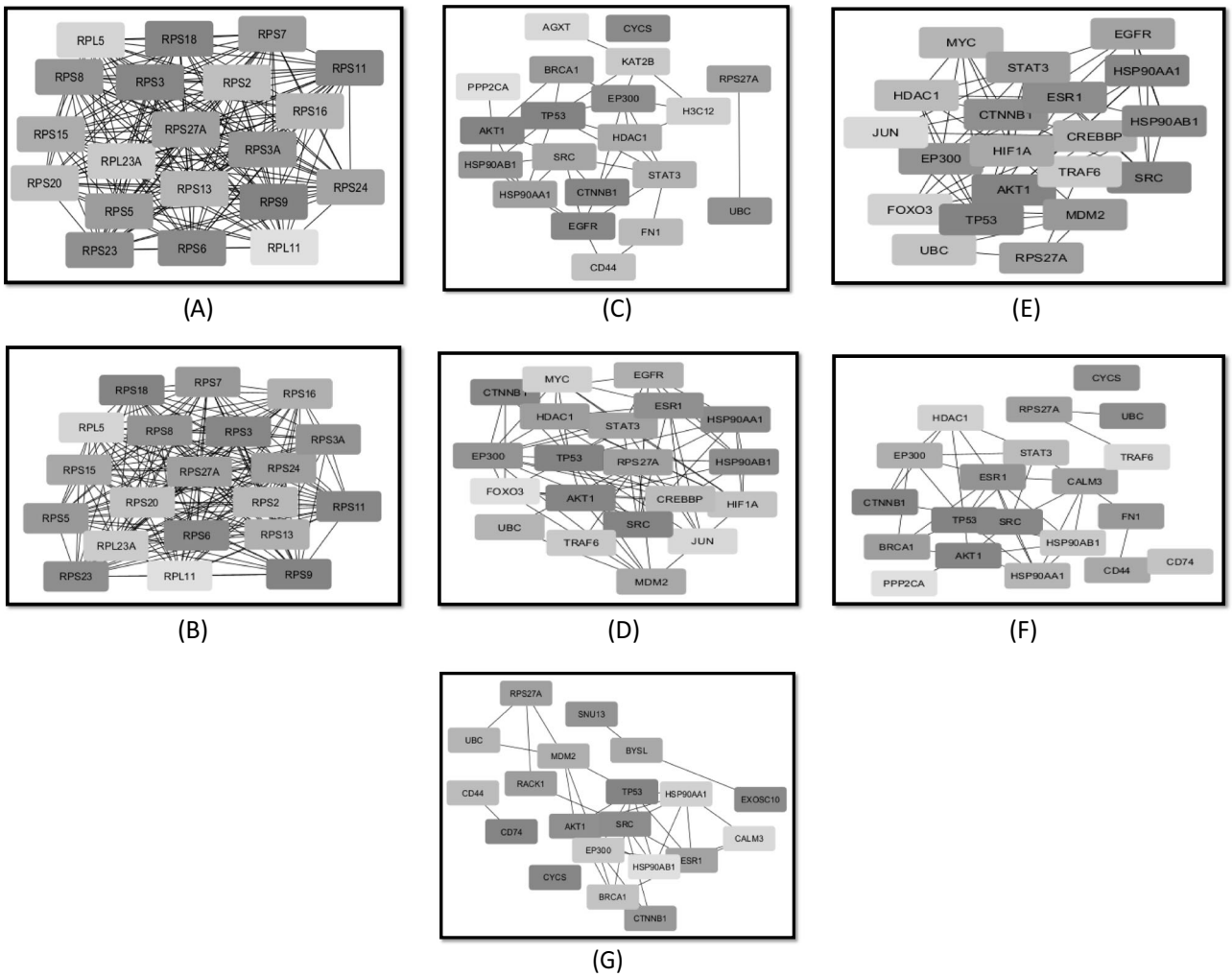


Fig. 4 Identification of the key hub gene RPS27A using Cytohubba analysis. The CytoHubba plugin in Cytoscape was used to identify the top 20 hub genes within the network based on 12 topological parameters. This figure visualizes the network according to seven of these parameters where the RPS27A gene was consistently identified as a significant hub. These parameters are **A** MNC, **B** degree, **C** bottleneck, **D** closeness, **E** radiality, **F** betweenness and **G** stress respectively.

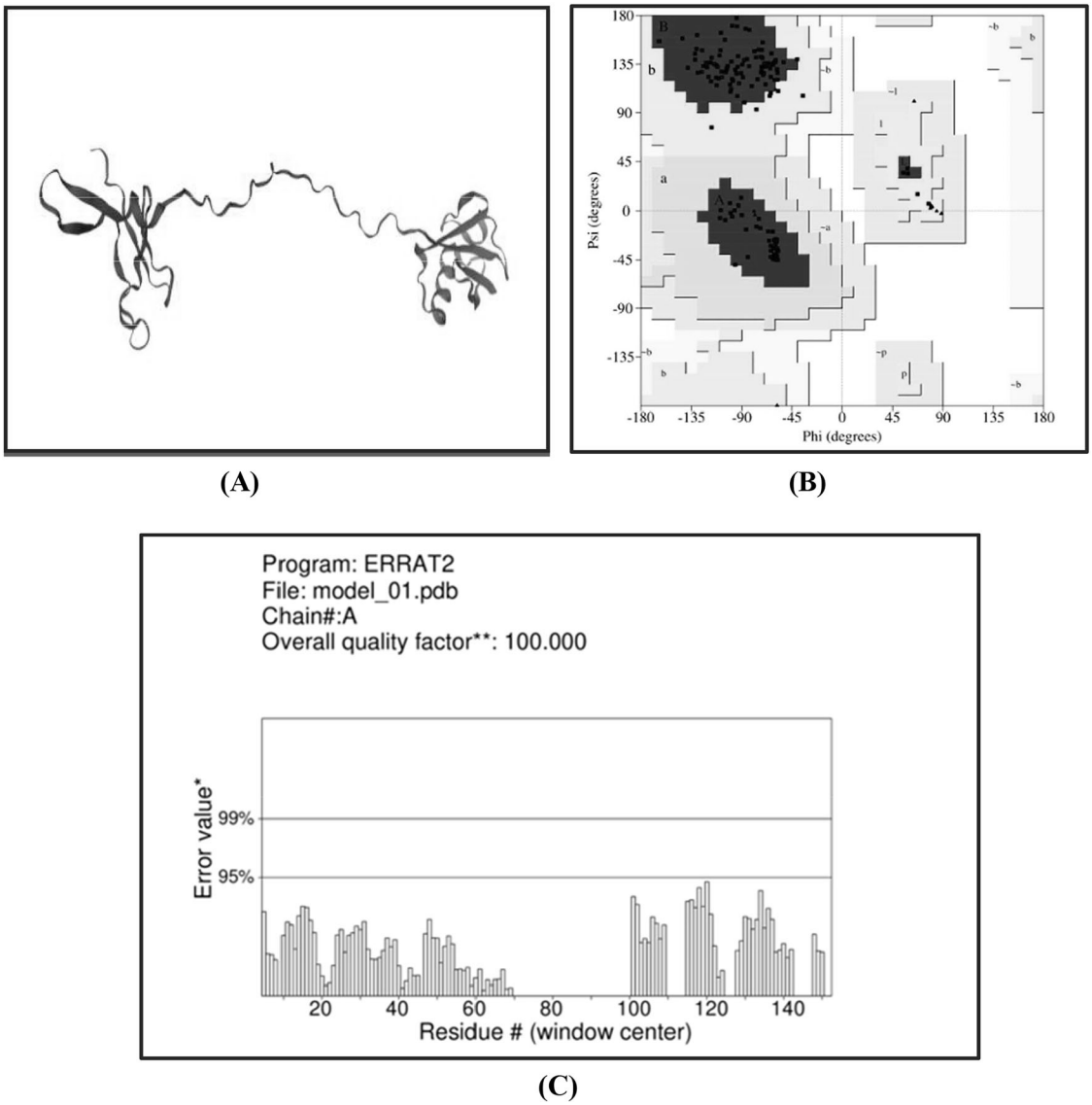


Fig. 5 Protein modelled structure & validation. A Modelled structure RPS27A receptor. **B** Ramachandran plot RPS27A receptor generated by procheck server. **C** Plot of error frequency produced by the ERRAT server.

interaction of miRNAs with RPS27A gene in five brain disorders were determined as shown in Fig. 7.

Effect analysis of phytocompound on miRNA expression

The effect of naringenin on the expression of miRNAs regulated in different brain disorders was analysed through the PSRR tool as depicted in Fig. 8. The down-regulation model's recommendation rate is 0.41, whereas the up-regulation model's proposal rate is 0.48. The small molecule-miRNA association shows that naringenin increases the expression of all the miRNAs involved in brain disorders except the lethal miRNA, that is, hsa-let-7a (rate = 0.392). The upregulation of miRNA by naringenin helps control the expression of the RPS27A gene, thereby, preventing its increased expression which is seen to be an important factor in hypertensive patients.

DISCUSSION

In the current study, systems biology highlights the significant role of **hsa-miR-21** in increasing the risk of neurological disorders in patients with hypertension. Through its regulation of inflammation, vascular dysfunction, and neurodegeneration, hsa-miR-21 contributes to conditions such as stroke, cognitive decline, and neuroinflammation. Studies suggest that miR-21 might influence the permeability of the blood-brain barrier (BBB), making it more susceptible to damage in hypertensive conditions [56].

In this study, we have seen that has-miR-21 is in close association with the neurological pathways associated with the RPS27A gene. Through network pharmacology approach RPS27A was identified as the key target gene. Hypergeometric tests were done the has-miR-21 and RPS27A gene to get the neurological diseases involved. Further, five neurological diseases were identified that are Acute cerebral infarction, Autism specific disorder (ASD), Parkinson's disease, Ependymoma and ACTH-Secreting pituitary adenoma, miR-21 is known to be dysregulated. Since RPS27A is involved in stress responses, its expression may be linked to miR-21 levels in these diseases.

Further, the network of RPS27A with all the five mentioned neurological diseases were made. After analyzing the networks, miRNA 21 was found common in four of the disease pathways except for ependymoma. Hypertensive patients with overexpression of hsa-miR-21 are at increased risk of ischemic stroke due to compromised vascular integrity. Plasma miR-21 levels are initially

Table 2. Table illustrating phytochemicals' binding energies with RPS27A receptor.

Phytochemical Name	Binding Energy	Amino Acid Residues
Naringenin	−6.28	Y105, Y140, V130, F131, A133, G129, C141, G142, G129, M132
Berberine	−6.05	K97, K99, V98, R95, L100,
Curcumin	−4.88	K78, K79, K81, K80, K82
Quercetin	−5.87	E120, P122, S123, D124, C126, R119, G127
Resveratrol	−4.71	T7, L8, I36, L69, L71, V70, E34
Anthocyanin	−5.23	F136, D137, F150, K152
Metformin	−3.61	C121, C126, D124, P122, S123
Ellagic acid	−5.26	K33, K11, T14, E34, I13A
Genistein	−5.65	Y85, T86, T87, P88, K90, K89
Puerarin	−4.84	K90, S84, T86, T87, Y85
Silybin	−5.48	Y85, T86, K89, S84, T87, K90, P88
Hydroxytyrosol	−4.16	I13, K33, T12, K11, E34, T14, K11
Betaine	−2.99	K29, K33, E16, L18
Piperine	−6.1	K83, K89, K90, Y85, S84, T86
Catechin	−5.21	K80, K81, K82, K83, R80, Y85
Silymarin	−5.48	Y85, T86, K89, S84, T87, K90, P88
Hydroxybenzoic acid	−5.11	K83, Y85, S84, T86,
Allicin	−3.15	L8, T9, I36, L71, L8
Capsaicin	−4.09	K78, K79, K81, K83, K82, K84, K80
Sulforaphane	−3.93	T7, T9, E34, L69, L8

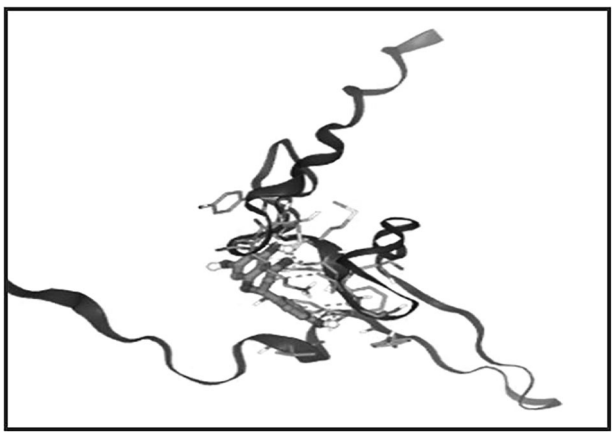


Fig. 6 Predicted molecular interaction between RPS27A and Naringenin. This figure illustrates the computationally predicted molecular interaction of Naringenin with the RPS27A protein, which exhibited the highest binding energy score of –6.28 kcal/mol in the docking analysis.

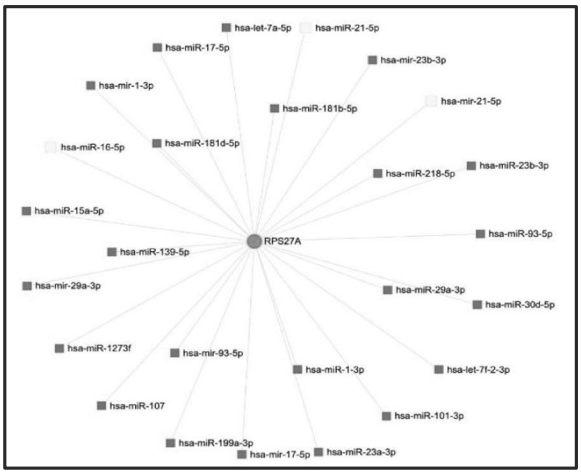
Table 3. List of neurological disease pathways regulated by the miRNAs interacting with RPS27A gene.

Pathway	P value	FDR
Acute Cerebral Infarction	0.00179	0.00199
Autism Spectrum Disorder	7.38E-07	8.20E-06
Parkinson's Disease	0.000842	0.00107
Ependymoma	0.00179	0.00199
ACTH-Secreting Pituitary Adenoma	6.87E-05	0.000172

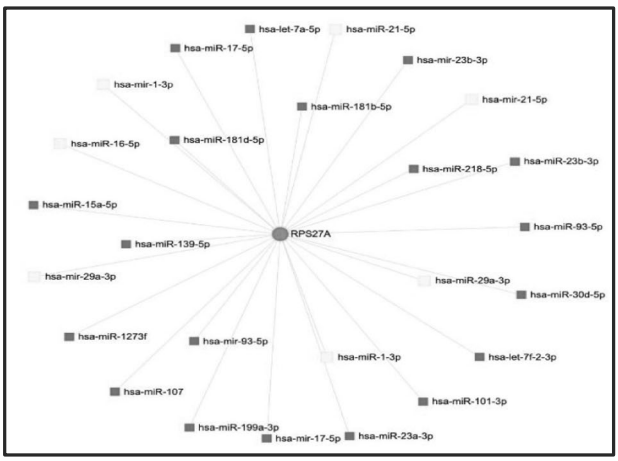
low in early-stage acute ischemic stroke (AIS) and negatively correlate with National Institute of Health Stroke Scale scores on the first day. However, miR-21 levels increase in the following days and may remain elevated for an extended period and further leads to

Table 4. Occurrence of hsa-miR-21-5p in different neurological disorders.

Disease	miRNA targets
Acute cerebral infarction	hsa-mir-21-5p
	hsa-miR-21-5p
	hsa-miR-16-5p
Autism specific disorder	hsa-miR-15a-5p
	hsa-mir-93-5p
	hsa-miR-23a-3p
	hsa-miR-93-5p
	hsa-miR-23b-3p
	hsa-mir-21-5p
	hsa-mir-23b-3p
	hsa-miR-21-5p
Parkinson's diseases	hsa-mir-1-3p
	hsa-miR-16-5p
	hsa-mir-29a-3p
	hsa-miR-1-3p
	hsa-miR-29a-3p
	hsa-mir-21-5p
	hsa-miR-21-5p
Ependymoma	hsa-miR-29a-3p
	hsa-mir-29a-3p
	hsa-miR-15a-5p
ACTH-Secreting Pituitary Adenoma	hsa-mir-21-5p
	hsa-miR-21-5p
	hsa-let-7a-5p
	hsa-miR-16-5p
	hsa-miR-15a-5p

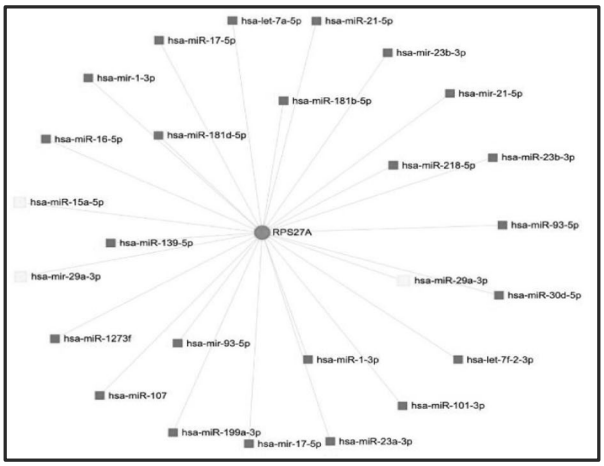


(Acute cerebral infarction)

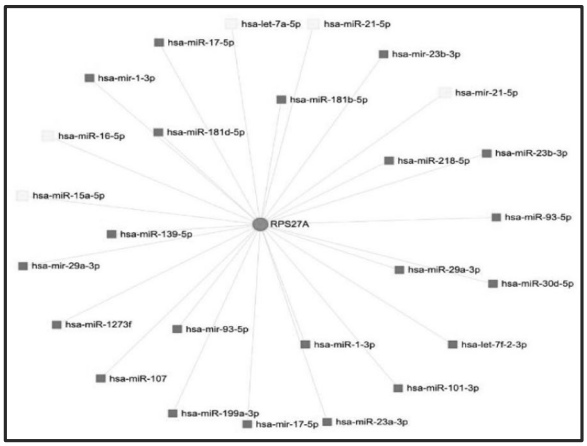


(Parkinson's diseases)

(Autism specific disorder)



(Ependymoma)



(ACTH-Secreting Pituitary Adenoma)

Fig. 7 Regulatory network of miRNAs targeting the RPS27A gene across various brain disorders. This figure depicts the predicted interactions between various microRNAs (miRNAs) and the RPS27A gene in the context of different brain disorders.

cerebral infarction [57]. Similarly, serum miR-21 levels are significantly elevated in patients with stroke and atherosclerosis [58].

Also, the miR-21-5p, derived from pre-miR-21, is linked to ASD by targeting and inhibiting Oxytocin receptor (OXTR) translation. Its overexpression in the ASD brain may worsen symptoms by reducing OXTR levels [59, 60]. Parkinson's disease (PD) affects 1–2 per 1000 people, with prevalence increasing to 1% in those over 60 years of age (59). It results from dopaminergic neuron degeneration in the substantia nigra and is linked to aging, pesticides, family history, and environmental toxins [61]. In PD,

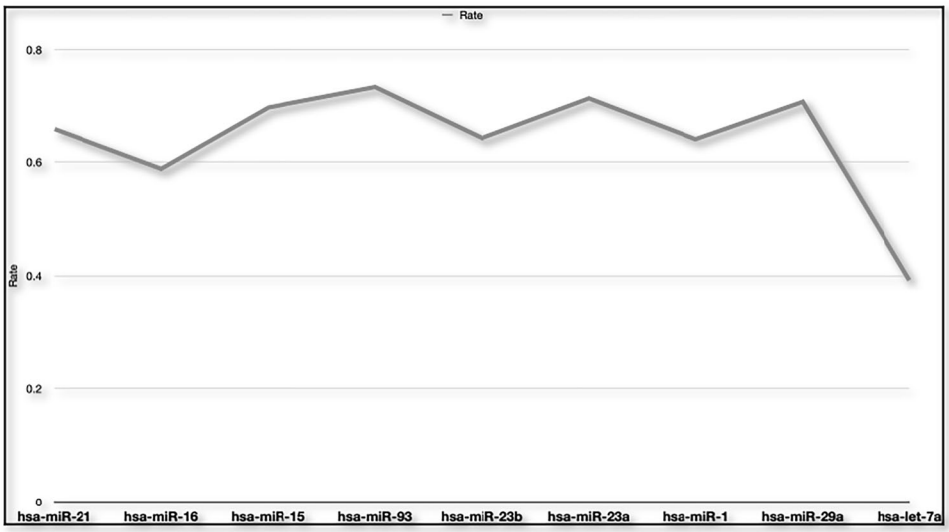


Fig. 8 Naringenin upregulates brain disorder-linked miRNAs, potentially regulating RPS27A. PSRR analysis indicates naringenin increases the expression of miRNAs involved in brain disorders, including hsa-let-7a, which may help control RPS27A expression.

miR-21 is elevated, while PPARα, a neuroprotective factor, is reduced. miR-21 directly targets PPARα's 3′ UTR, suggesting that miR-21 downregulation could help restore PPARα levels and protect neurons [62].

Later, the effect of naringenin was seen on the miRNAs. Naringenin showed the best binding energy score of −6.28 with RPS27A. It is a natural flavonoid having neuroprotective activities [63]. According to reports, naringenin is readily absorbed by the gastrointestinal tract, making it quickly accessible in the bloodstream. It is the most pharmacologically efficacious version of naringin due to its quick absorption [64]. Naringenin's capacity to scavenge free radicals produced under a variety of baseline metabolic circumstances has been linked to its therapeutic actions, which include the suppression of oxidative stress [65]. By addressing neuroinflammation and dopaminergic neuroprotection, naringenin has demonstrated potential in the treatment of Parkinson's disease (PD) [66]. So, naringenin can target the miRNAs associated with neurological disorders.

Lastly, the effect of naringenin on the miRNAs were predicted to check the regulation. The small molecule-miRNA association shows that naringenin increases the expression of all the miRNAs involved in brain disorders except the lethal miRNA (hsa-let-7a). This signifies that naringenin helps in regulating the expression of RPS27A. Consequently, its elevated expression is inhibited, which is thought to be a significant factor in hypertension people. Therefore, understanding the role of hsa-miR-21 in neurological disorders in hypertensive patients opens the possibility for therapeutic interventions. Targeting miR-21 using anti-miR strategies could reduce its harmful effects, providing a novel approach for treating neurological conditions linked to hypertension.

SUMMARY

What is known about the topic

- Hypertension significantly increases the risk of neurological disorders such as stroke, dementia, and Parkinson's disease.
- MicroRNAs (miRNAs) play a critical role in gene expression regulation, especially in neurological and cardiovascular conditions.
- The miRNA hsa-miR-21 is associated with inflammation, vascular dysfunction, and neurodegeneration, which can exacerbate neurological disorders in hypertensive patients.

What this study adds

- The study identified RPS27A as a key target gene associated with hypertension through a systems biology approach.
- Naringenin, a natural phytochemical, exhibited strong molecular interaction with RPS27A, suggesting its potential in regulating miRNA expression linked to neurological disorders.
- The regulation of hsa-miR-21 by naringenin indicates a promising therapeutic approach for mitigating neurological risks in hypertensive patients.

DATA AVAILABILITY

The National Center for Biotechnology Information (www.ncbi.nlm.nih.gov) has the data utilized in this investigation.

REFERENCES

1. Li Z, Chyr J, Jia Z, Wang L, Hu X, Wu X, et al. Identification of hub genes associated with hypertension and their interaction with miRNA based on weighted gene coexpression network analysis (WGCNA) analysis. Med Sci Monit. 2020;26:e923514.
2. Iqbal AM, Jamal SF. Essential Hypertension. [Updated 2023 Jul 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539859/.
3. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. JAMA. 2017;317:165–82.
4. GBD 2016 Risk Factors Collaborators: "Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016". Lancet. 2016;390:1345–1422.
5. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. Nat Genet. 2017;49:403–15.
6. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Dominiczak AF, et al. Hypertension. Nat Rev Dis Primers. 2018;4:18014.
7. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16:223–37.
8. Kelly DM, Rothwell PM. Blood pressure and the brain: the neurology of hypertension. Pract Neurol. 2020;20:100–8.
9. Loewenstein D, Rabbat M. Neurological complications of systemic hypertension. Handb Clin Neurol. 2021;177:253–9.
10. Wang JG, Li Y. Primary and secondary prevention of stroke by antihypertensive drug treatment. Expert Rev Neurother. 2004;4:1023–31.

11. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet. 1990;335:827–38.
12. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet. 2000;355:865–72.
13. Turana Y, Shen R, Nathaniel M, Chia YC, Li Y, Kario K. Neurodegenerative diseases and blood pressure variability: A comprehensive review from HOPE Asia. J Clin Hypertens (Greenwich). 2022;24:1204–17.
14. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017;389:37–55.
15. Zhai Z, Tao X, Alami MM, Shu S, Wang X. Network pharmacology and molecular docking combined to analyse the molecular and pharmacological mechanism of pinellia ternata in the treatment of hypertension. Curr Issues Mol Biol. 2021;43:65–78.
16. Ventura HO, Lavie CJ. Editorial. Curr Opin Cardiol. 2019;34:329–30.
17. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365:217–23.
18. Di Palo KE, Barone NJ. Hypertension and Heart Failure. Heart Fail Clin. 2020;16:99–106.
19. Fan H, Lu F, Yang A, Dong Y, Liu P, Wang Y. A review on the nonpharmacological therapy of traditional Chinese medicine with antihypertensive effects. Evid Based Complement Altern Med. 2019;2019:1–7.
20. Pistoia F, Sacco S, Degan D, Tiseo C, Ornello R, Carolei A. Hypertension and stroke: epidemiological aspects and clinical evaluation. High Blood Press Cardiovasc Prev. 2016;23:9–18.
21. Schmieder RE. End organ damage in hypertension. Dtsch Aerzteblatt Online. 2010;107:866–73.
22. Fagard R, Brguljan J, Staessen J, Thijs L, Derom C, Thomis M, et al. Heritability of conventional and ambulatory blood pressures. A study in twins. Hypertension. 1995;26:919–24.
23. Guyton AC, Coleman TG, Cowley AW, Scheel KW, Manning RD, Norman RA. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med. 1972;52:584–94.
24. Shaheen N, Shaheen A, Diab RA, Desouki MT. MicroRNAs (miRNAs) role in hypertension: pathogenesis and promising therapeutics. Ann Med Surg (Lond). 2023;86:319–28.
25. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136:215–33.
26. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. Science. 2001;294:853–8.
27. Yu D-C, Li Q-G, Ding X-W, Ding Y-T. Circulating microRNAs: potential biomarkers for cancer. Int J Mol Sci. 2011;12:2055–63.
28. Jang JH, Lee T-J. The role of microRNAs in cell death pathways. Yeungnam Univ J Med. 2021;38:107–17.
29. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension. Hypertension. 2021;77:692–705.
30. Campana E, Cunha V, Glaveckaite S, Gruev I, Lamirault G, Lehmann E, et al. The use of single-pill combinations as first-line treatment for hypertension: translating guidelines into clinical practice. J Hypertens. 2020;38:2369–77.
31. Tsioufis K, Kreutz R, Sykara G, van Vugt J, Hassan T. Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: a rapid evidence assessment of recent literature. J Hypert. 2020;38:1016–28.
32. Wang H-B, Yang J. The role of renin-angiotensin aldosterone system related micro-ribonucleic acids in hypertension. Saudi Med J. 2015;36:1151–5.
33. Ma J, Chen X. Advances in pathogenesis and treatment of essential hypertension. Front Cardiovasc Med. 2020;9:1003852.
34. Delles C, Husi H. Systems biology approach in hypertension research. Methods Mol Biol. 2017;1527:69–79.
35. Chandran U, Mehendale N, Patil S, Chaguturu R, Patwardhan B. Network pharmacology. Innovative Approaches in Drug Discovery. 2016;127–164. https://doi.org/10.1016/B978-0-12-801814-9.00005-2.
36. Kibble M, Saarinen N, Tang J, Wennerberg K, Mäkelä S, Aittokallio T. Network pharmacology applications to map the unexplored target space and therapeutic potential of natural products. Nat Prod Rep. 2015;32:1249–66.
37. Cho D-Y, Kim Y-A, Przytycka TM. Chapter 5: network biology approach to complex diseases. PLoS Comput Biol. 2012;8:e1002820.
38. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol. 2008;4:682–90.
39. Ellingson SR, Smith JC, Baudry J. Polypharmacology and supercomputer-based docking: opportunities and challenges. Mol Simul. 2014;40:848–54.
40. Rappaport N, Twik M, Plaschkes I, Nudel R, Iny Stein T, Levitt J, et al. Mala Cards: an amalgamated human disease compendium with diverse clinical and genetic annotation and structured search. Nucleic Acids Res. 2017;45:D877–D887.
41. Safran M, Dalah I, Alexander J, Rosen N, Iny Stein T, Shmoish M, et al. Gene Cards Version 3: the human gene integrator. Database (Oxford). 2010;2010:baq020.
42. Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, et al. The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic Acids Res. 2020;48:845.
43. Hamosh A, Scott AF, Amberger JS, Bocchini CA, McKusick VA. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res. 2005;33:514–7.
44. Clough E, Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, et al. NCBI GEO: archive for gene expression and epigenomics data sets: 23-year update. Nucleic Acids Research. 2024; 52:D138–D144.
45. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 2003;13:2498–504.
46. UniProt Consortium. UniProt: the universal protein knowledgebase in 2021. Nucleic Acids Res. 2021;49:D480–D489.
47. Schwede T, Kopp J, Guex N, Peitsch MC. SWISS-MODEL: An automated protein homology-modelling server. Nucleic Acids Res. 2003;31:3381–5.
48. Wlodawer A. Stereochemistry and validation of macromolecular structures. Methods Mol Biol. 2017;1607:595–610.
49. Colovos C, Yeates TO. Verification of protein structures: Patterns of non-bonded atomic interactions. Protein Sci. 1993;2:1511–9.
50. Hollingsworth SA, Karplus PA. A fresh look at the Ramachandran plot and the occurrence of standard structures in proteins. Biomol Concepts. 2010;1:271–83.
51. Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, et al. PubChem Substance and Compound databases. Nucleic Acids Res. 2016;44:D1202–D1213.
52. Murail S, de Vries SJ, Rey J, Moroy G, Tufféry P. SeamDock: An Interactive and Collaborative Online Docking Resource to Assist Small Compound Molecular Docking. Front Mol Biosci. 2021;8:716466.
53. Murail S, de Vries SJ, Rey J, Moroy G, Tufféry P. Seam Dock: an interactive and collaborative online docking resource to assist small compound molecular docking. Front Mol Biosci. 2021;8:716466.
54. Chang L, Zhou G, Soufan O, Xia J. miRNet 2.0: network-based visual analytics for miRNA functional analysis and systems biology. Nucleic Acids Res. 2020;48:W244–W251.
55. Yu F, Li B, Sun J, Qi J, De Wilde RL, Torres-de la Roche LA, et al. PSRR: a web server for predicting the regulation of miRNAs expression by small molecules. Front Mol Biosci. 2022;9:817294.
56. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013;1:e259–e281. https://doi.org/10.1016/S2214-109X(13)70089-5.
57. Zhou J, Zhang J. Identification of miRNA-21 and miRNA-24 in plasma as potential early stage markers of acute cerebral infarction. Mol Med Rep. 2014;10:971–6. https://doi.org/10.3892/mmr.2014.2245.
58. Tsai PC, Liao YC, Wang YS, Lin HF, Lin RT, Juo SHH. Serum microRNA-21 and microRNA-221 as potential biomarkers for cerebrovascular disease. J Vasc Res. 2013;50:346–54. https://doi.org/10.1159/000351767.
59. Mor M, Nardone S, Sams DS, Elliott E. Hypomethylation of miR-142 promoter and upregulation of microRNAs that target the oxytocin receptor gene in the autism prefrontal cortex. Mol Autism. 2015;6:46 https://doi.org/10.1186/s13229-015-0040-1.
60. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm. 2017;124:901–5.
61. Beitz JM. Parkinson's disease: a review. Front Biosci. 2014;6:65–74. https://doi.org/10.2741/s415.
62. Fu Y, Zhen J, Lu Z. Synergetic neuroprotective effect of docosahexaenoic acid and aspirin in SH-Y5Y by inhibiting miR-21 and activating RXRα and PPARα. DNA Cell Biol. 2017;36:482–9. https://doi.org/10.1089/dna.2017.3643.
63. Nouri Z, Fakhri S, El-Senduny FF, Sanadgol N, Abd-ElGhani GE, Farzaei MH, et al. On the neuroprotective effects of naringenin: pharmacological targets, signaling pathways, molecular mechanisms, and clinical perspective. Biomolecules. 2019;9:690. https://doi.org/10.3390/biom9110690.
64. Mir IA, Tiku AB. Chemopreventive and therapeutic potential of "naringenin," a flavanone presents in citrus fruits. Nutr Cancer. 2015;67:27–42. https://doi.org/10.1080/01635581.2015.976320.
65. Zaidun NH, Thent ZC, Latiff AA. Combating oxidative stress disorders with citrus flavonoid: Naringenin. Life Sci. 2018;208:111–22. https://doi.org/10.1016/j.lfs.2018.07.017.
66. Chen C, Wei YZ, He XM, Li DD, Wang GQ, Li JJ, et al. Naringenin produces neuroprotection against LPS-Induced dopamine neurotoxicity via the inhibition of microglial NLRP3 inflammasome activation. Front Immunol. 2019;10:936. https://doi.org/10.3389/fimmu.2019.00936.

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AUTHOR CONTRIBUTIONS

SM performed data curation, formal analysis, and wrote the original draft. PG contributed to the methodology, interpretation of results, and participated in reviewing and editing the draft. MT reviewed the final version of the manuscript. PS supervised the study and contributed to the review and editing of the final draft. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with relevant guidelines and regulations. Ethical approval was not required for this study as it involved only computational analyses of publicly available datasets and did not involve human participants or live vertebrates. Therefore, informed consent was not applicable.

ADDITIONAL INFORMATION

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