Integrated Network Pharmacology and *In-Silico* Molecular Docking Studies to Unveil Mechanism of Action of Polyphenolic Compounds of *Psidium Guajava* for The Management of Thrombocytopenia

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Abstract: Despite considerable studies, thrombocytopenia is still affecting millions of people with an increasing rate of morbidity and mortality around the globe. Therefore, we aimed to identify pharmacologically active polyphenolic compounds such as quercetin, apigenin and kaempferol in *Psidium guajava* for the management of thrombocytopenia using network pharmacology and *in-silico* molecular docking. The results of ADME/Tox screening revealed that all the polyphenolic compounds possess the drug-likeness activity and were found safe. Moreover, network pharmacology revealed that polyphenolic compounds of *Psidium guajava* may combat diabetes by acting on key targets, such as MAPK, TP53 and TNF-α which were strongly involved in oxidative stress, inflammatory responses and blood-related parameters involved in thrombocytopenia. Further, a mechanistic approach through molecular docking also supports the strong binding sites of quercetin, apigenin and kaempferol. Conclusively, *in-silico* ADME, molecular docking and network pharmacology study revealed that identified compounds are safe and pharmacologically effective. These identified compounds could be a great source for the development of new anti-thrombocytopenic drugs in the future.

Keywords: *Psidium Guajava*, Polyphenol, Network Pharmacology, Docking, Anti-Thrombocytopenic

1. Introduction

Dengue fever is one of the most rapidly changing viral infections that possess a threat to human life and economics all over the world. Dengue fever has been on the rise in recent years all across the world (Ahmad et al., 2021). Dengue fever affects almost 390 million people each year. According to a report, dengue fever cases were reported to be 2.2 million by the World Health Organization in 2021. Dengue fever primarily weakens the immune system of the body.

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The most prevalent symptoms connected with it were observed to be headache, hypertension, mental illness, inflammation, liver disease and thrombocytopenia with or without bleeding and inflammation. The liver causes severe bleeding, which might lead to death (Ahmad et al., 2019).

Furthermore, thrombocytopenia is a condition in which the number of thrombocytes, also known as platelets, is reduced. Viral infections, pharmacological side effects, radiation, vitamin insufficiency, tumour infiltration, and bone marrow failure syndrome are all common causes of thrombocytopenia (Reardon and Marques, 2006).

In today's world, there is a growing interest in identifying novel herbal medicines or phytopharmaceuticals that can be used to treat thrombocytopenia and are regarded as a viable alternative to modern allopathic medications (Ahmad et al., 2019). *Psidium guajava* L., for example, is a member of the Myrtaceae family and has traditionally been used to treat hyperlipidemia, insulin resistance, diabetes mellitus, cardiovascular diseases, microbial infection, cancer, liver disorders, and antidiarrheal action (Sanda et al., 2011; Daswani et al., 2017).

Herbal medicine or formulations containing many plants are commonly employed, and these complex chemical mixes contain numerous possible bioactive components that can interact with a variety of therapeutic targets. This multi-component, multi-target, and multi-pathway approach may be ideal for treating diseases with a complex pathophysiology and therapeutic targets, but it also poses a significant challenge in terms of understanding the interactions between different components, their mechanisms of action, and molecular targets (Jiang et al., 2019). Network pharmacology and *in-silico* molecular docking studies may play an important role to unveil the pharmacological action of bioactive compounds (Ren et al., 2020). Through the interaction of compound-compound, compound-target, and target-disease, it might be used to elucidate the synergistic effects among compounds and probable mechanisms of multi-component and multiple target drugs at the molecular level. The study of complicated formulations might benefit from network pharmacology and *in-silico* docking, which would make it easier to comprehend the relationships between chemicals, genes, proteins, and diseases (Hong et al., 2020).

Moreover, computational methods of pharmacological screening of lead compounds reduce the cost of the experiment, time-consumption in discovery and most importantly minimize the number of investments and frillier at any stage of drug development of bioactive leads from a huge loss to the organization (Huang et al., 2020; Li et al., 2014). Network pharmacology, however, systemically analyzing drugs and drug targets may provide us with novel insights into drug actions. As a useful tool for systematically evaluating and demonstrating the rationality of drugs, it has now been widely accepted. Keeping in view, the present study aims to explore the enzyme inhibitory effect of *Psidium guajava* and reveals its mechanism by utilizing network pharmacology and *in-silico* molecular docking studies.

2. Material and Methods

2.1 Plant Materials and Chemicals

Fresh leaves were obtained from the herbal garden of Jamia Hamdard and the hydroethanolic extract was prepared for polyphenolic and antioxidant analysis.

2.2 Determination of Total Phenol and Flavonoids

The total phenol content was determined using the Folin Ciocalteu (FC) technique with some changes. In a nutshell, an extract stock solution in methanol (5 mg/mL) was made. 2.5 mL FC (1:10, v/v) was added to a 500 ml stock solution. 2.5 mL of 7.5 percent sodium bicarbonate solution was added after mixing, and the mixture was left for 30 minutes with intermittent shaking. The absorbance at 765 nm was measured using a spectrophotometer. To determine total phenolic content, a calibration curve was plotted between absorbance and standard values, and the result was expressed as mg gallic acid equivalent/gm of extract (mg GAE/ gm extract). The total flavonoid concentration was determined using a modified aluminium chloride technique. In methanol, a stock solution of extract at 5 mg/mL was produced. 1.5 mL methanol was added to a 500 µL stock solution. 0.1 mL aluminium chloride (10%), 0.1 mL sodium acetate (1M), and 2.8 mL water were added after 5 minutes. A spectrophotometer was used to detect absorbance at 415 nm after 30 minutes of incubation. To determine total phenolic content, a calibration curve was drawn between absorbance and concentrations of reference quercetin, and the result was expressed as mg quercetin equivalent/gm extract (mg quercetin/ gm extract) (Madaan et al., 2011).

2.3 Antioxidant Activities

According to the methodology, the extract's ability to scavenge DPPH (2, 2-diphenyl-1-picrylhydrazyl) was examined. The samples were mixed with a 0.1 mM DPPH solution and incubated at 37°C for 30 minutes in the dark. The scavenging potential was calculated using absorbance at 517 nm. Quercetin was used as a control ingredient (Fahim et al., 2019).

2.4 ADME/Tox Analysis of the Lead Compounds

Using literature and a database, the polyphenolic compounds were discovered. SwissADME and ProTox-II were also used to determine the compounds' drug-likeness and toxicity qualities. According to Lipinski's rule of five ADME/Tox characteristics dictate the drug-like activity of ligand molecules. The SMILES (Simplified Molecular Input Line Entry System) of chemicals were identified using PubChem (https://pubchem.ncbi.nlm.nih.gov/). Following that, target information for active chemicals in moth beans was obtained from a variety of databases, including the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (https://lsp.nwu.edu.cn/). The target names were entered into the UniProt database (http://www.uniprot.org/) with the species "Homo sapiens" selected, and the target gene names were retrieved from the UniProt database.

2.5 In-silico Molecular Docking

2.5.1 Active Site Prediction

The active site was anticipated using the Pymol software's site discovery function. From the 3D atomic coordinates of the receptor, the site finder function was utilized to compute probable active sites for all the selected enzymes. To find probable sites for ligand binding and docking, as well as limitation sets for rendering incomplete molecular surfaces, calculations were performed.

2.5.2 Preparation of Targeted Enzyme and Molecular Docking

With Auto Dock, all polar hydrogen atoms were added to the target enzyme, while water molecules and other heteroatoms were removed. Gasteiger charges were added to the ligands, and all rotatable bonds were made rotatable. Using Autodock 4.2, the optimized ligand molecules were docked with refined diabetes receptors. Pymol, a molecular graphics visualization programme, was used to examine

the docking data. Following the completion of docking searches, the optimal conformation with the lowest binding energy was chosen from the most populated cluster (Jackie et al., 2018)

2.5.3 Target Genes Related to Selected Compounds and Thrombocytopenia

Swiss Target Prediction (STP) (http://www.swisstargetprediction.ch/) with "Homo Sapiens" mode was used to choose target genes connected to the chemicals based on the SMILES. DisGeNET (https://www.disgenet.org/search) discovered genes linked to diabetes mellitus.

2.5.4 Protein-Protein Interaction (PPI) Network Construction

The target proteins of related constituents of moth beans were uploaded to the STRING (http://string-db.org) online website to gather information on protein-protein interaction to explain the interaction between target proteins (PPI). For mutual knowledge of target proteins, the website generated a score. The higher the score, the more certain you can be in the interaction between target proteins. As a result, in this study, we chose high confidence data >0.7 to ensure that the analysis is reliable. To create a PPI protein interaction network, the collected protein interaction data were imported into the Cytoscape 3.2.1 software. Furthermore, we built a network between disease and essential genes implicated in the pathophysiology of thrombocytopenia and its associated disorders.

2.5.5 Gene Ontology and KEGG Enrichment Analysis of Target Proteins

The shiny was used to evaluate the Gene Ontology function and KEGG pathway enrichment of proteins engaged in the PPI network to elucidate the role of target proteins that interact with the bioactive chemicals of moth beans in gene function and signaling pathway. The pathways and target proteins involved in the biological process (BP) were also outlined.

3. Result and Discussion

3.1 Total Phenolic and Flavonoid Content Estimation

The calibration curves of gallic acid (r2 = 0.9901) and quercetin (r2 = 0.9907) were used to evaluate total phenolic and flavonoid content. Total phenolic and flavonoid concentrations were found to be 59.06 ± 0.41 mg equivalents per gram of gallic acid and 78.35 ± 0.54 mg equivalents per gram of quercetin, respectively.

3.2 Assay for Scavenging Free Radicals

The ability to scavenge the DPPH radical was measured in percentage inhibition. DPPH screening of moth beans revealed dose-dependent antioxidant activity at the various doses tested (10-250 µg/mL) in this study. Psidium guajava and quercetin have 78.65 percent and 91.24 percent inhibitory potential, respectively, at the highest concentrations tested. The results showed that the antioxidant inhibition of moth beans is equivalent to that of the reference chemical.

3.3 ADME/Tox Analysis

Rapid results from server-based ADME/Tox analysis could be important in the development of lead compounds (Hari, 2019). For the ADME analysis of the substances in our investigation, we used Swissdock. Table 1 summarizes the findings, whereas Figure 1 depicts the docking diagram. All of the polyphenolic compounds' predicted qualities meet all of Lipinski's five requirements, indicating that

they have drug-like potential. All of the substances studied have good solubility and absorption in the human intestine. During the design of a pharmacological molecule, it is vital to forecast the situation and movement of the medication in the human body. The bioavailability radar provides a quick assessment of a molecule's drug-likeness by taking into account six physicochemical qualities such as LIPO (Lipophilicity), SIZE, POLAR (Polarity), INSOLU (Insolubility), INSATU (Insaturation) and FLEX (Flexibility) respectively.

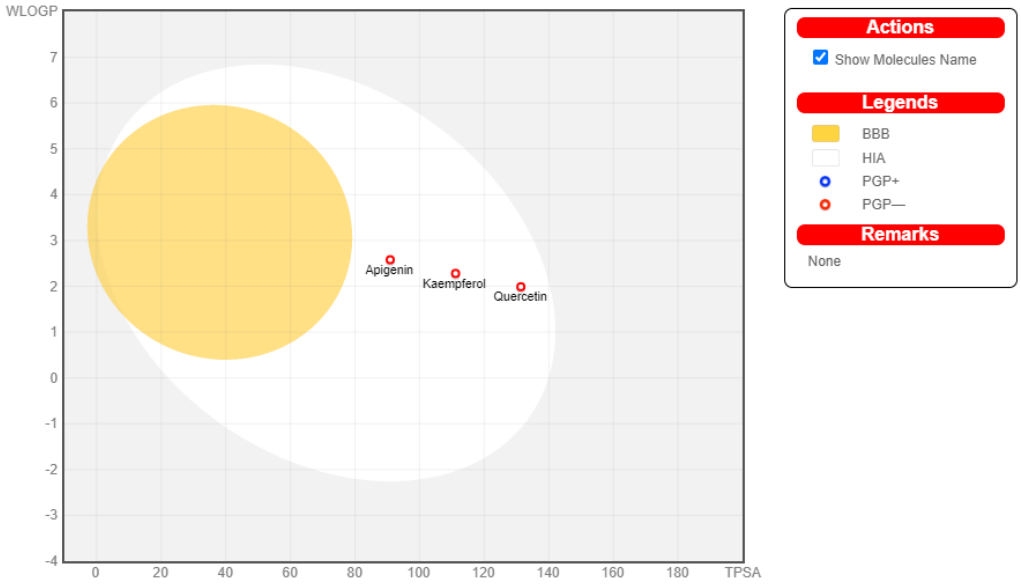
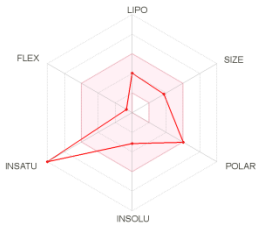
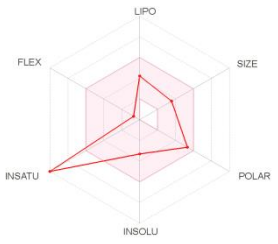
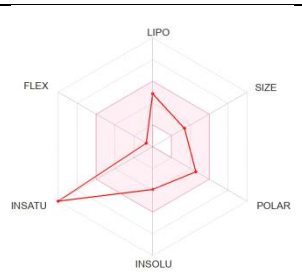


Figure 1: Boiled-Egg representation of the polyphenolic compounds for the drug-likeness studies.

Table 1: Swiss ADME profiling of selected polyphenolic compounds.

Name of metabolites	Lipinski Violation	Bioavailability radar	Bioavailability score	Ali Class	GI absorption
Quercetin	0		0.55	Soluble	High
Kaempferol	0		0.55	Soluble	High

Apigenin	0		0.55	Soluble	High

The quercetin, kaempferol and apigenin were found to be non-hepatotoxic in a toxicity class ranging from 1 (toxic) to 6 (non-toxic) (Table 2). Toxicity in close proximity to one is thought to be more harmful to human health, and vice versa. The ADME/Tox characteristics play a significant role in drug filtering throughout the early phases of drug development (Yi et al., 2018).

Table 2: Prediction of toxicity of polyphenolic compounds computed by Pro-Tox II.

Name of metabolites	LD 50(mg/kg)	ToxicityClass	Hepatotoxicity
Quercetin	159	3	No
Kaempferol	3919	5	No
Apigenin	2500	5	No

3.4 Molecular Docking Analysis

AutoDock is a popular platform for studying the interaction of a protein with its ligand or inhibitor. The interaction of quercetin, apigenin, and kaempferol with human proteins such as TNF-α, MAPK, and TP53 was investigated using molecular docking. The types of chemical interactions produced and the binding locations of amino acid residues revealed the ligand-protein interaction. Figure 2 shows the overall molecular docking results of all the compounds.

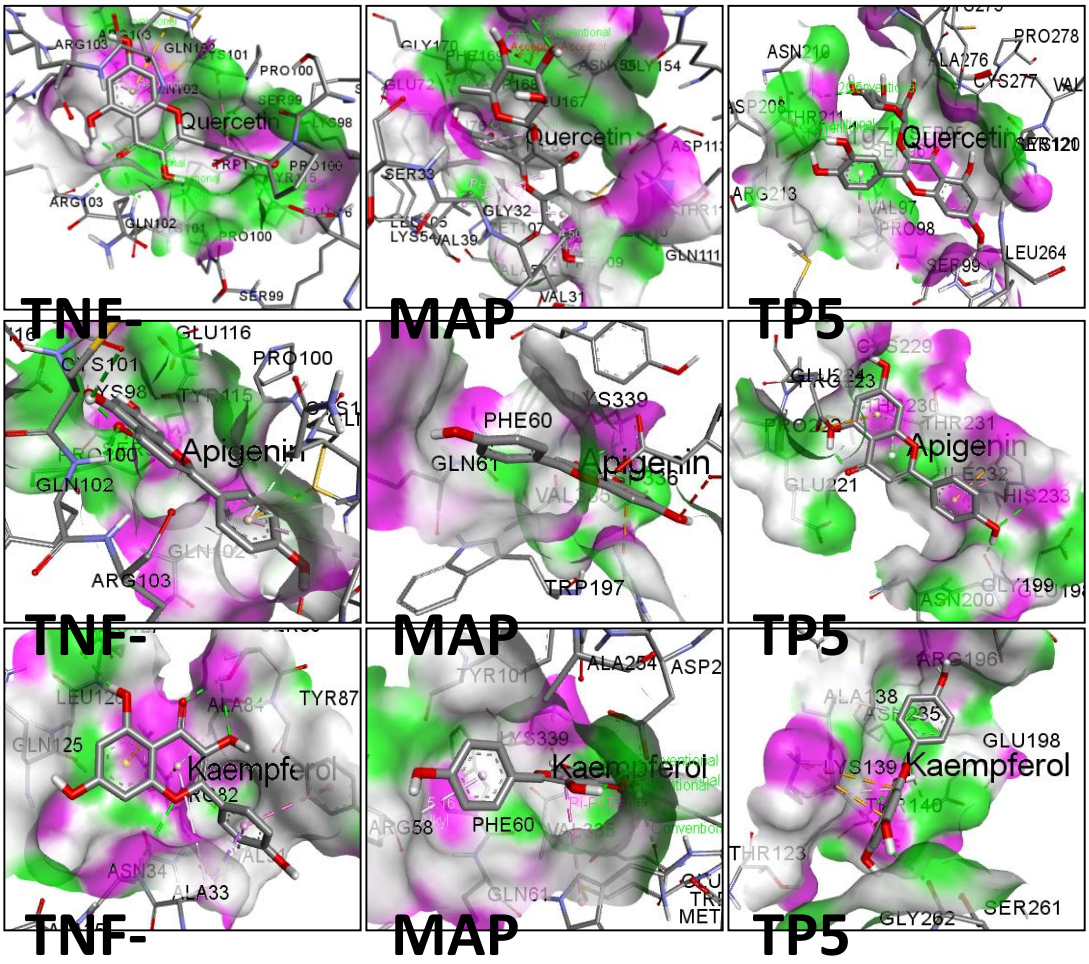


Figure 2: 3D binding interaction of quercetin, apigenin and kaempferol with the enzymes TNF-α, MAPK, and TP53, respectively.

3.4.1 Target Genes and Disease Association Network

We used the Network Analyst to build a target-disease interaction network (Figure 3) and evaluated thrombocytopenic and associated disease and pathways including 48 target proteins to better understand the relationship between target proteins and disease association. Numerous target proteins exist in one pathway, while the same target protein exists in multiple pathways, according to network analysis. In essence, a pathway that involves numerous target proteins is more important than a pathway that involves only one target protein. These findings imply that the active pharmacological components in Psidium guajava may act on thrombocytopenia-related signalling pathways.

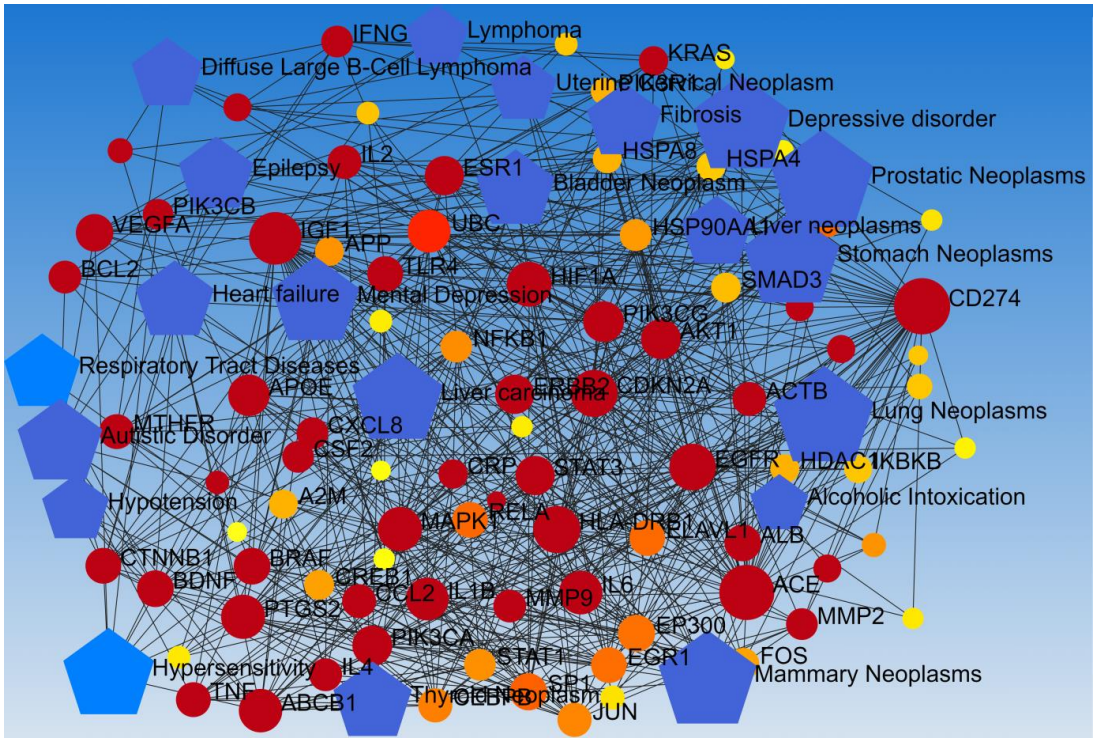


Figure 3: Targets-disease interaction analysis. The blue color represents the disease and the rest shows the target genes.

3.4.2 PPI Network of Targeted Genes and Understanding the Action Mechanisms of Bioactive Compounds

The STRING was used to examine the selected possible gene targets, and the PPI network was created (Figure 4). The networking graphic depicts the intimate relationships that exist between genes. Furthermore, we chose biopotential genes TNF-α, MAPK, and TP53) from the same PPI network to reveal the action mechanism of Psidium guajava possibly bioactive substances (quercetin, apigenin, and kaempferol). The compound-target-pathway network was depicted in Figure 5 clearly displayed the chemical mechanism of all polyphenolic substances. Figure 5 suggested the existence of highly complex correlations between different bioactive compounds and target genes, as well as an understanding of complex network relationships in terms of "one ingredient-multiple target" and "multiple ingredient-multi target" relationships.

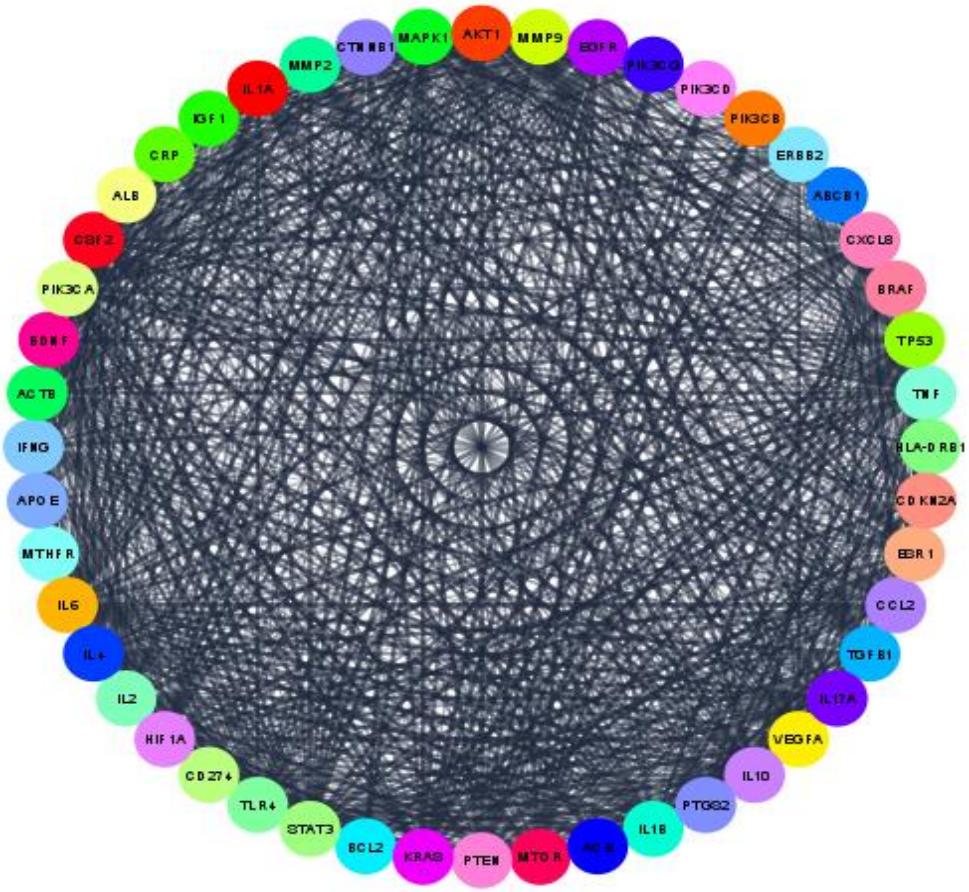


Figure 4: Protein-protein interactions of diabetes-related gene targets of the polyphenolic compounds of Psidium guajava. Outer side nodes are considered as most important genes involved in the progression of thrombocytopenia.

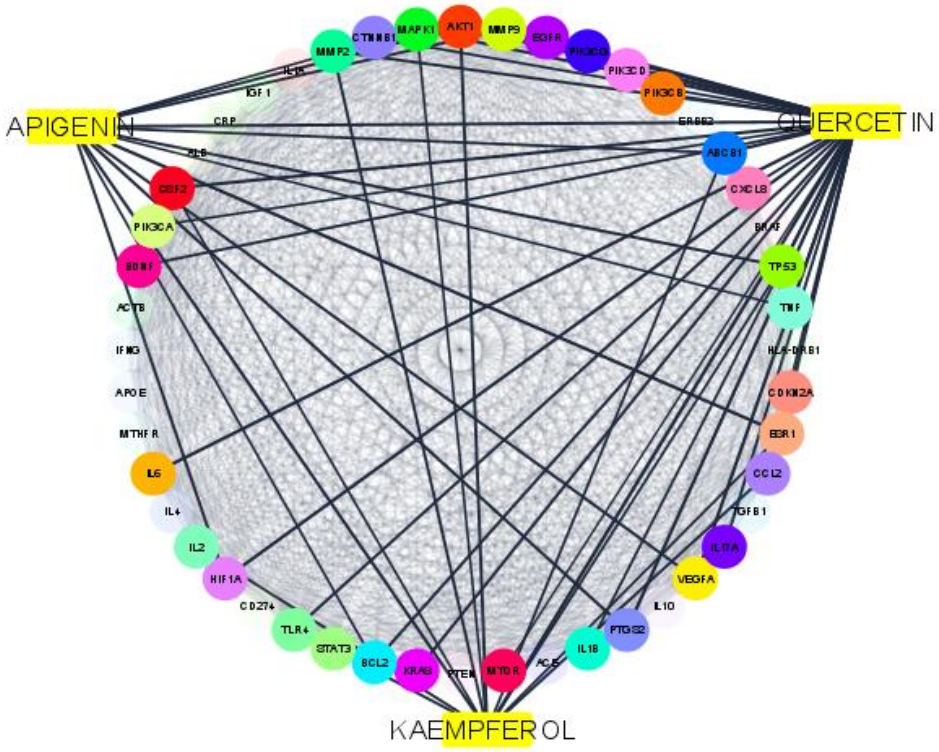


Figure 5: The polyphenolic compound-target-pathway network of Psidium guajava.

3.4.3 GO Analysis and KEGG Enrichment Analysis of Target Genes

The biological process results suggested that these targets participated in various pathways including cell death, T cell activation, etc. Whereas Figure 6 clearly represented that KEGG enrichment signaling pathways are involved in various signaling pathways involved in various disease and disorders

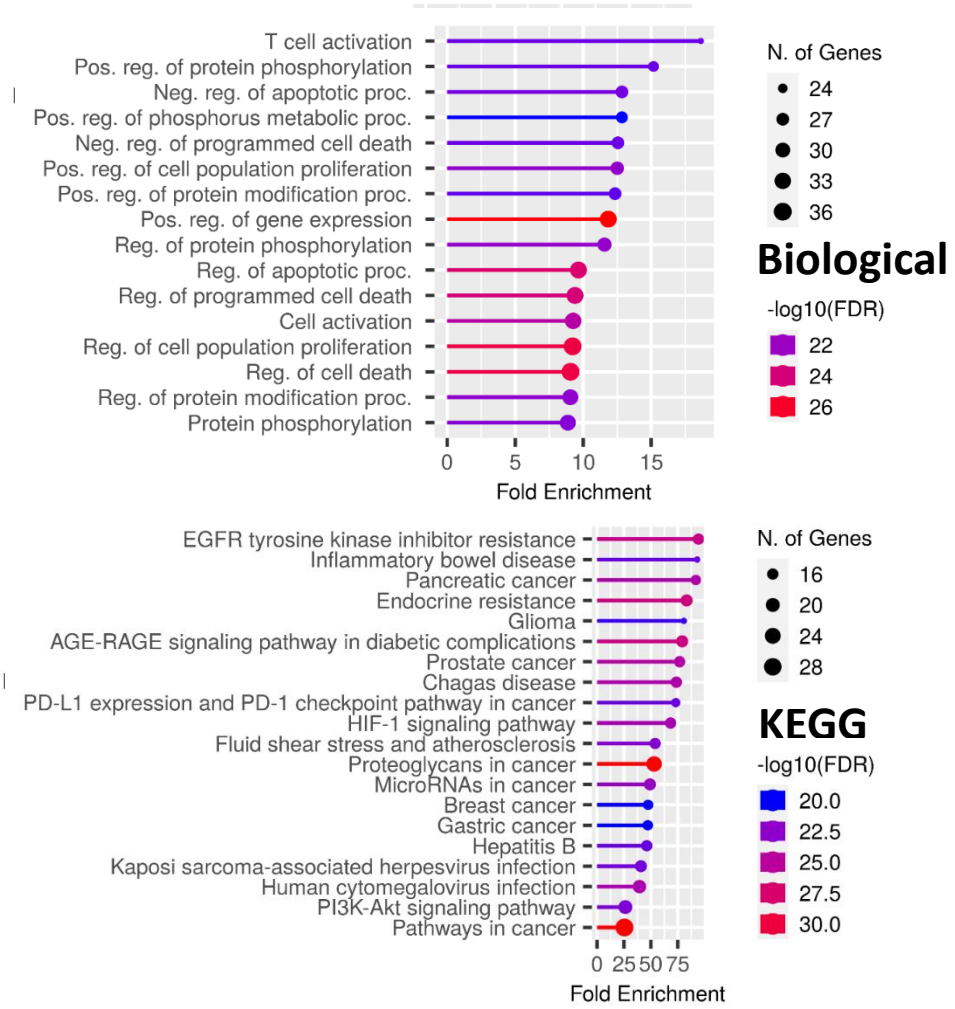


Figure 6: GO biological process and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of potential target genes of polyphenolic compounds. The color from red to blue indicates the decreasing fold enrichment value, greater the value, the higher the significance of the pathway.

Herbal medicine is a unique medical idea that has been established and manufactured for thousands of years in Asian countries for the treatment and prevention of illnesses. To increase therapeutic impact through synergism, complex herbal preparations with numerous appropriate plants are routinely used(Pan et al., 2014). The failure of the spleen to control blood is thought to be the cause of thrombocytopenia. Thrombocytopenia is another clinical sign of dengue virus infection, which is common in both moderate and severe cases. Platelets drop below the normal range of 150,000-450,000 platelets per liter of blood and can drop as low as 40,000 platelets per liter of blood. Another sign is an increased flow of blood into mucous membranes, especially during menstruation (Izak and Bussel, 2014).

Consumption of polyphenols has a long history of use in the treatment of chronic diseases including thrombocytopenia and its consequences, according to growing data (Vauzour et al., 2010). Using network pharmacology and experimental research, polyphenolic chemicals from Psidium guajava were used to highlight the understanding of drug action across several levels of information in this study. The network pharmacology of bioactive compounds and target proteins is an important

technique to characterize the pharmacological mechanism of bioactive compounds that can be used to research and design new drugs in the future. Network pharmacology is a well-accepted strategy to find the disease target, bioactive hit molecules, and regulated pathways via "many component-protein interactions" due to the composite nature of bioactive compounds in leaves of Psidium guajava (Li et al., 2017; Chandran et al., 2017).

Polyphenols with anti-thrombocytopenic properties were chosen for this study. Currently, we discovered that all of these bioactive substances had therapeutic effects on platelet loss by acting on many pathways involved in thrombocytopenia, based on network pharmacology research (Vauzour et al., 2010). The three compounds (quercetin, kaempferol and apigenin) and 48 target genes were used to create a compound-target network in this investigation. Quercetin worked on multiple targets, according to the findings (Figure 7). Despite the fact that the number of potential targets varied in the case of each compound and interestingly lots of targets are overlapping (Chu et al., 2022). To put it another way, numerous three molecules may share the same target, resulting in synergistic effects. Polyphenols have multiple components, targets, and pathways. As a herbal medicine, Psidium guajava has the same property. As a result, it's safe to assume that Psidium guajava tackles thrombocytopenia in a multi-pathway manner. All three compounds synergistically act on the key proteins involved in thrombocytopenia like TNF-α, MAPK, and TP53. MAPKs affect gene expression, immunological response, cell proliferation, apoptosis, and oxidative stress response, which is one of the immune regulation mechanisms (Qu et al., 2018). Thrombocytopenia has been linked to tumor necrosis factor α (TNF-α) medications. Cited study suggested that TP53 signaling pathway is involved in thrombocytopenia or PLT diseases. In addition, in-silico molecular studies of quercetin, apigenin and kaempferol interacted with the active sites of the enzyme TNF-α, MAPK, and TP53, showing excellent inhibition of enzyme activity (Ibrahim et al., 2022; Johnson et al., 2011). The interactions between proteins and ligands showed strong hydrogen bindings. These confirm that compounds contained in the extracts of Psidium guajava scan be used as anti-thrombocytopenic candidates.

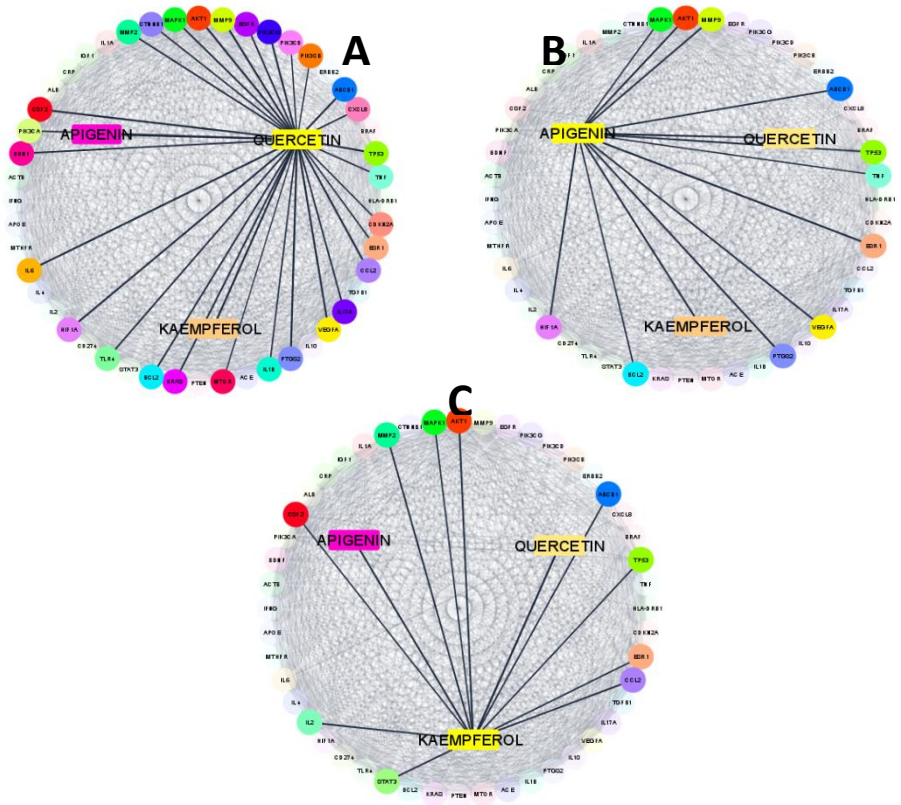


Figure 7: Interaction of individual compounds on the key targets. These compounds show synergistic activity by interacting with same compounds as clearly shown in the figure.

4. Conclusion

Network pharmacology and in-silico docking studies demonstrated that Psidium guajava has an excellent ability to manage the thrombocytopenic effect by acting on enzymes involved in thrombocytopenia TNF-α, MAPK, and TP53. In summary, we can conclude that this strategy can be considered as fast and high-confidence method for screening natural compounds in the extract for the management of various diseases and disorders.

References

Ahmad, A., Ibrahim, M., Ansari, S. H., Taleuzzaman, M., and Ahmad, S. (2021). Antithrombocytopenic potential of metabolically characterized extract and fractions of Momordica charantia L. fruits by in vivo study. *Ann. Phytomedicine An Int. J.* 10, doi: 10.21276/ap.2021.10.2.35.

Ahmad, A., Ibrahim, M., Chester, K., Khan, W., Ahmad, S., and Ansari, S. (2019). Antithrombocytopenic potential of bioactivity guided fractions of traditionally used Psidium guajava Linn. leaves in busulfan induced-thrombocytopenic rats. *Pharmacogn. Mag.* 15, 440, doi: 10.4103/pm.pm_608_18.

Jackie, B., Sagar, S., Alamgir, H., Razowanul, Md.F., Sumaiya, F., et al. (2018) In silico Molecular Docking and ADME/T Analysis of Some Selected Isolated Compounds of *Phyllanthus emblica* against Type 2 Diabetics. *Am J Ethnomed*, 5(2), 3–7, doi: 10.21767/2348-9502.100009.

Chandran, U., Mehendale, N., Patil, S., Chaguturu, R., and Patwardhan, B. (2017). "Network Pharmacology," in *Innovative Approaches in Drug Discovery: Ethnopharmacology, Systems Biology and Holistic Targeting*, doi: 10.1016/B978-0-12-801814-9.00005-2.

Chu, M., Gao, T., Zhang, X., Kang, W., Feng, Y., Cai, Z., et al. (2022). Elucidation of Potential Targets of San-Miao-San in the Treatment of Osteoarthritis Based on Network Pharmacology and Molecular Docking Analysis. *Evidence-based Complement. Altern. Med*, doi: 10.1155/2022/7663212.

Daswani, P. G., Gholkar, M. S., and Birdi, T. J. (2017). Psidium guajava: A single plant for multiple health problems of rural Indian population. *Pharmacogn. Rev.* 11, 167–174, doi: 10.4103/phrev.phrev_17_17.

Fahim, M., Ibrahim, M., Zahiruddin, S., Parveen, R., Khan, W., Ahmad, S., et al. (2019). TLC-bioautography identification and GC-MS analysis of antimicrobial and antioxidant active compounds in Musa × paradisiaca L. fruit pulp essential oil. *Phytochem. Anal*, doi: 10.1002/pca.2816.

Hong, Z., Duan, X., Wu, S., Yanfang, Y., and Wu, H. (2020). Network Pharmacology Integrated Molecular Docking Reveals the Anti-COVID-19 Mechanism of Qing-Fei-Da-Yuan Granules. *Nat. Prod. Commun.* 15, doi: 10.1177/1934578X20934219.

Huang, Q., Liu, R., Liu, J., Huang, Q., Liu, S., and Jiang, Y. (2020). Integrated network pharmacology analysis and experimental validation to reveal the mechanism of anti-insulin resistance effects of moringa oleifera seeds. *Drug Des. Devel. Ther*, doi: 10.2147/DDDT.S265198.

Ibrahim, M., Parveen, B., Zahiruddin, S., Gautam, G., Parveen, R., Khan, M. A., et al. (2022). Analysis of polyphenols in Aegle marmelos leaf and ameliorative efficacy against diabetic mice through restoration of antioxidant and anti-inflammatory status. *J. Food Biochem*, 46. doi: 10.1111/jfbc.13852.

Izak, M., and Bussel, J. B. (2014). Management of thrombocytopenia. *F1000Prime Rep.* 6, doi: 10.12703/P6-45.

Jiang, Y., Liu, N., Zhu, S., Hu, X., Chang, D., and Liu, J. (2019). Elucidation of the mechanisms and molecular targets of Yiqi Shexue formula for treatment of primary immune thrombocytopenia based on network pharmacology. *Front. Pharmacol*, 10. doi: 10.3389/fphar.2019.01136.

Johnson, J. L., Rupasinghe, S. G., Stefani, F., Schuler, M. A., and Gonzalez De Mejia, E. (2011). Citrus flavonoids luteolin, apigenin, and quercetin inhibit glycogen synthase kinase-3β enzymatic activity by lowering the interaction energy within the binding cavity. *J. Med. Food* ,14, 325–333. doi: 10.1089/jmf.2010.0310.

Li, H., Zhao, L., Zhang, B., Jiang, Y., Wang, X., Guo, Y., et al. (2014). A network pharmacology approach to determine active compounds and action mechanisms of Ge-Gen-Qin-Lian decoction for treatment of type 2 diabetes. *Evidence-based Complement. Altern. Med*, doi: 10.1155/2014/495840.

Li, W., Yuan, G., Pan, Y., Wang, C., and Chen, H. (2017). Network pharmacology studies on the bioactive compounds and action mechanisms of natural products for the treatment of diabetes mellitus: A review. *Front. Pharmacol*, doi: 10.3389/fphar.2017.00074.

Madaan, R., Bansal, G., Kumar, S., and Sharma, A. (2011). Estimation of total phenols and flavonoids in extracts of Actaea spicata roots and antioxidant activity studies. *Indian J. Pharm. Sci*, 73, 666–669. doi: 10.4103/0250-474X.100242.

Pan, S. Y., Litscher, G., Gao, S. H., Zhou, S. F., Yu, Z. L., Chen, H. Q., et al. (2014). Historical perspective of traditional indigenous medical practices: The current renaissance and

conservation of herbal resources. *Evidence-based Complement. Altern. Med*. doi: 10.1155/2014/525340.

Qu, X., Tang, Y., and Hua, S. (2018). Immunological approaches towards cancer and inflammation: A cross talk. *Front. Immunol.* 9. doi: 10.3389/fimmu.2018.00563.

Reardon, J. E., and Marques, M. B. (2006). Evaluation of thrombocytopenia. *Lab. Med*, 37, 248–250. doi: 10.1309/R7P79KERAJHPRHLT.

Ren, W., Luo, Z., Pan, F., Liu, J., Sun, Q., Luo, G., et al. (2020). Integrated network pharmacology and molecular docking approaches to reveal the synergistic mechanism of multiple components in venenum bufonis for ameliorating heart failure. *PeerJ*, 8. doi: 10.7717/peerj.10107.

Sanda, K. A., Grema, H. A., Geidam, Y. A., and Bukar-Kolo, Y. M. (2011). Pharmacological aspects of Psidium guajava: An Update. *Int. J. Pharmacol*, 7, 316–324. doi: 10.3923/ijp.2011.316.324.

Vauzour, D., Rodriguez-Mateos, A., Corona, G., Oruna-Concha, M. J., and Spencer, J. P. E. (2010). Polyphenols and human health: Prevention of disease and mechanisms of action. *Nutrients*. doi: 10.3390/nu2111106.

Yi, F., Li, L., Xu, L. jia, Meng, H., Dong, Y. mao, Liu, H. bo, et al. (2018). In silico approach in reveal traditional medicine plants pharmacological material basis. *Chinese Med. (United Kingdom)*. doi: 10.1186/s13020-018-0190-0.