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Mapping the Therapeutic Potential of *Persicaria minor* Phytochemicals Against Oxidative Stress: A Target-Centric Network Approach

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ABSTRACT

Oxidative stress underlies the pathogenesis of chronic disorders through the dysregulation of redox-sensitive signalling. Yet, the molecular mechanisms underlying the antioxidant capacity of *Persicaria minor* remain poorly understood. This study integrated pharmacokinetic filtering, target prediction, and topological network analysis to elucidate the systems-level antioxidant mechanisms of *P. minor*. Among 143 reported phytoconstituents, 27 exhibited favourable oral bioavailability and interacted with 152 oxidative stress–related targets. Network metrics identified isorhamnetin, feruloyltyramine, and radiclonic acid as central bioactives targeting key regulators including NOX4, XDH, and CA2 (degree ≥ 30). Functional enrichment revealed modulation of the PI3K–AKT, MAPK, and p53 pathways—central nodes of the oxidative stress response. These findings provide mechanistic insights into *P. minor*'s redox-modulatory potential and position it as a promising candidate for the development of multi-target antioxidant therapeutics.

1. Introduction

Oxygen-free radicals act as signalling molecules but can cause harm when overproduced, especially during stress. Excess reactive oxygen and nitrogen species (ROS/RNS) disrupt the redox balance, causing oxidative stress associated with diseases such as cardiovascular issues, neurodegeneration, diabetes, and cancer [1]. Antioxidation, the process of neutralising or inhibiting oxidative reactions induced by ROS, represents one of the body's crucial defence mechanisms. In recent decades, the discovery of natural antioxidants from medicinal plants has attracted substantial scientific interest due to their biocompatibility, reduced toxicity, and therapeutic potential [2]. Within this context, *Persicaria minor* (synonym: Polygonum minus Huds.), a member of the Polygonaceae family, has emerged as a significant source of antioxidant and anti-inflammatory agents [3].

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Persicaria minor is a small, aromatic herb that is widely distributed in Southeast Asia, particularly in Malaysia, Indonesia, Thailand (known as *phak pai*), and Vietnam [4]. Locally known as "kesum," it has a long history of culinary and ethnomedicinal use. Its leaves are valued as flavouring ingredients in traditional dishes such as *ulam* and *laksa*, and decoctions of its leaves have been used to alleviate digestive ailments, headaches, and dandruff [5]. Beyond its culinary applications, *P. minor* has been pharmacologically documented to exhibit diverse bioactivities, including antioxidant, anti-ulcer, analgesic, antibacterial, anti-inflammatory, and cytotoxic effects, as well as inhibition of platelet aggregation and low-density lipoprotein oxidation [6]. These properties are primarily attributed to its abundance of bioactive secondary metabolites, notably flavonoids, anthraquinones, and terpenoids, which collectively modulate redox balance and inflammatory processes [7,8].

The high antioxidant potential of *P. minor* has been observed in aqueous, methanolic, and ethanolic extracts, primarily due to the presence of phenolic and flavonoid compounds [9]. However, although the individual biological activities of its constituents have been documented, a critical knowledge gap remains in understanding how these phytochemicals act synergistically through molecular networks to regulate oxidative stress. Traditional biochemical assays and single-compound evaluations provide valuable information but fail to capture the complex multi-target nature of plant-derived therapeutics.

In recent years, network pharmacology has emerged as a powerful systems-level approach to elucidate the collective mechanisms of natural compounds within biological networks [10]. Unlike reductionist methods that assess single active constituents, network pharmacology integrates pharmacokinetic filtering, molecular target prediction, and topological analysis to map the compound–target–pathway relationships underpinning therapeutic effects. This paradigm has successfully clarified the antioxidant mechanisms of plants such as *Curcuma longa*, *Camellia sinensis*, and *Ginkgo biloba* [11–13]. Yet, despite the well-documented bioactivity of *P. minor*, no comprehensive network-level analysis has been undertaken to decipher its underlying antioxidant or redox-modulatory mechanisms.

Therefore, this study applies an integrative, target-centric network pharmacology framework to map the molecular interactions of *P. minor* phytochemicals against oxidative stress–related targets. Specifically, the objectives are to (i) identify key active compounds with favourable pharmacokinetic profiles; (ii) construct and analyse the compound–target–pathway network to determine hub nodes and biological significance; and (iii) elucidate the mechanistic roles of these bioactives in modulating oxidative stress. It is hypothesised that the antioxidant potential of *P. minor* arises from the synergistic regulation of multiple redox-related signalling pathways rather than from isolated compound effects.

Unlike previous investigations that focused primarily on chemical profiling or docking of single constituents, this study integrates multi-database phytochemical retrieval, ADME-based drug-likeness screening, and network-level mapping to deliver a unified, systems-level understanding of *P. minor*'s bioactivity. This holistic approach provides mechanistic insight into how *P. minor* phytochemicals collectively influence redox homeostasis and disease-relevant pathways, offering a foundation for the rational development of plant-based antioxidant therapeutics.

2. Methodology

2.1 Compound Identification

Phytoconstituents of *Persicaria minor* were systematically gathered through searches of ScienceDirect, Scopus, and PubMed using the keywords "Persicaria minor" OR "Polygonum minus". Reported constituents were further verified and standardised across multiple phytochemical

databases, including IMPPAT 2.0, PubChem, KNApSAcK, Dr Duke's Phytochemical and Ethnobotanical Database, and the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP). Duplicates and entries not derived from plants were manually removed. The final list of compounds was annotated with PubChem CID identifiers and cross-checked for antioxidant or redox-modulatory activities reported in the literature.

2.2 Pharmacokinetic Screening (ADME Analysis)

To ensure pharmacological relevance, all retrieved compounds were subjected to *in silico* pharmacokinetic evaluation using the SwissADME tool. Screening followed a tiered protocol: (i) drug-likeness assessment based on Lipinski's Rule of Five, excluding compounds with ≥ 2 violations [9], (ii) oral bioavailability (OB) threshold set at ≥ 0.55 to ensure adequate gastrointestinal absorption [10], (iii) compounds were further filtered for non-penetration of the blood–brain barrier (BBB), high gastrointestinal absorption (HIA), and exclusion as P-glycoprotein (PGP) substrates, as PGP efflux reduces intestinal bioavailability [11] and (iv) potential inhibition of major cytochrome P450 (CYP) isoforms, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 was evaluated to minimise the risk of metabolic interference [12]. Only compounds satisfying all ADME and toxicity criteria were retained for subsequent target prediction. This filtration ensured that the shortlisted phytochemicals exhibited favourable pharmacokinetic profiles, compatible with oral therapeutic applications.

2.3 Target Prediction and Disease-Related Gene Selection

Predicted molecular targets of each retained compound were obtained from SwissTargetPrediction using the *Homo sapiens* setting and a probability cut-off ≥ 0.1. Disease-associated targets were retrieved from GeneCards by querying the term "oxidative" and restricting the inclusion to entries with relevance scores greater than 1.0, focusing on oxidative-stress-related genes [13]. The compound-derived and disease-related target lists were intersected using a Venn-diagram approach implemented in Venny 2.0 to identify overlapping targets that may mediate the antioxidant effects of *P. minor*.

2.4 Network Visualisation and Topology Analysis

A compound–target interaction (CTI) network was generated using Cytoscape 3.10.2. Each compound and target protein were represented as a node, with edges denoting predicted interactions. Visual inspection and clustering were performed to highlight molecular connectivity patterns. Topological parameters were calculated using the CytoNCA plugin [14] to evaluate the structural importance of nodes within the network. Three primary metrics were employed: (i) degree centrality (DC) where number of direct interactions of a node, reflecting its connectivity, (ii) betweenness centrality (BC) in which frequency of a node on the shortest paths between all other nodes, indicating control over information flow and (iii) closeness centrality (CC): inverse of the average shortest path length from a node to all others, representing network accessibility. Thresholds for hub identification were set at DC ≥ average. Nodes exceeding this threshold were considered *hub compounds* or *hub targets*. These parameters quantify the systemic influence and integrative potential of each compound within the antioxidant network.

2.5 Functional and Pathway Enrichment

To elucidate the biological relevance of identified targets, Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) enrichment analyses were performed using ShinyGO database. Significance thresholds were set at $p < 0.05$ and false discovery rate (FDR) < 0.05 using Benjamini–Hochberg correction. Enriched pathways related to oxidative stress regulation, apoptosis, metabolism, and signal transduction were visualised using bubble plots and pathway maps.

3. Results

3.1 Identification and Pharmacokinetic Screening of the Compounds in Persicaria minor

Comprehensive data mining across five phytochemical databases and three scientific platforms (Scopus, ScienceDirect, and PubMed) yielded a total of 143 reported constituents of *Persicaria minor.* After removing duplicates and non-plant compounds, 131 unique compounds were retained. Application of ADME-based screening using SwissADME, with criteria of oral bioavailability (OB) ≥ 0.55 and adherence to Lipinski's Rule of Five, identified 128 pharmacologically suitable compounds. Subsequent filtering based on pharmacokinetic stability, specifically high gastrointestinal absorption, absence of blood–brain barrier (BBB) permeability, non-substrate status for P-glycoprotein (PGP), and limited inhibition of cytochrome P450 (CYP) isoforms, further refined the list to 27 bioactive compounds (Table 1). These candidates demonstrated favourable bioavailability and physicochemical characteristics consistent with oral therapeutic potential. Physicochemical profiling revealed that all selected compounds displayed acceptable partition coefficients (WlogP < 5), negative skin permeability values (log Kp < 0), and high intestinal permeability. None violated more than one of Lipinski's parameters, suggesting optimal molecular weight and hydrogen-bonding properties for cellular absorption and systemic distribution. These findings confirm that *P. minor* contains a diverse yet pharmacokinetically viable pool of bioactives, dominated by flavonoids, phenolic acids, and aromatic amides, compounds historically associated with antioxidant activity [15,16].

3.2 Target Prediction and Identification of Oxidative Stress–Related Genes

Of the 27 screened compounds, 22 were successfully mapped to 207 predicted molecular targets using the SwissTargetPrediction tool. Meanwhile, GeneCards retrieval with the keyword "oxidative" yielded 15,253 genes associated with oxidative stress responses. After relevance filtering (score > 1), 4,712 genes remained. The intersection of compound-derived and disease-related targets produced 152 overlapping genes (Figure 1), suggesting potential mediators of *P. minor*'s antioxidant activity. This overlap suggests that approximately 3.2% of all oxidative stress–related targets may be modulated by *P. minor* phytochemicals, highlighting the broad systemic influence of these compounds.

Table 1
27 Compounds identified in *Persicaria minor*

CID	Formula	Compounds	SMILES
9064	$C_{15}H_{14}O_6$	Catechin	Oc1cc2OC(c3ccc(c(c3)O)O)C(Cc2c(c1)O)O
5281654	$C_{16}H_{12}O_7$	Isorhamnetin	COc1cc(ccc1O)c1oc2cc(O)cc(c2c(=O)c1O)O
5280863	$C_{15}H_{10}O_6$	Kaempferol	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O
370	$C_7H_6O_5$	Gallic acid	OC(=O)c1cc(O)c(c(c1)O)O
19	$C_7H_6O_4$	2,3-Dihydroxybenzoic acid	OC(=O)c1cccc(c1O)O
72276	$C_{15}H_{14}O_6$	(−)-Epicatechin	Oc1cc2OC(c3ccc(c(c3)O)O)C(Cc2c(c1)O)O
689043	$C_9H_8O_4$	Caffeic acids	OC(=O)C=Cc1ccc(c(c1)O)O
260003	$C_9H_{14}O_4$	Carboxymethyl-cyclohexanecarboxylic acid	OC(=O)C1(CCCCC1)CC(=O)O
5280537	$C_{18}H_{19}NO_4$	Feruloyltyramine	COc1cc(C=CC(=O)NCCc2ccc(cc2)O)ccc1O
5280569	$C_9H_6O_4$	Daphnetin	O=C1CCC2C(O1)C(O)C(CC2)O
5281416	$C_9H_6O_4$	Esculetin	O=c1ccc2c(o1)cc(c(c2)O)O
361512	$C_{15}H_{10}O_6$	Citreorosein	OCc1cc(O)c2c(c1)C(=O)c1c(C2=O)c(O)cc(c1)O
10207	$C_{15}H_{10}O_5$	Aloe-emodin	OCc1cc(O)c2c(c1)C(=O)c1c(C2=O)c(O)ccc1
5281691	$C_{16}H_{12}O_7$	Rhamnetin	COc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O
5273755	$C_{18}H_{16}O_7$	Eupatilin	COc1cc(ccc1OC)c1cc(=O)c2c(o1)cc(c(c2O)OC)O
45359249	$C_{23}H_{40}O_5$	(2Z)-2-[(E)-6-(hydroxymethyl)-2,4,8,10-tetramethyldodec-2-enylidene]-4-methylpentanedioic acid	OCC(CC(C=C(C=C(C(=O)O)CC(C(=O)O)C)C)C)CC(CC(CC)C)C
5280343	$C_{15}H_{10}O_7$	Quercetin	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O
4650	$C_6H_4O_2$	p-benzoquinone	O=C1C=CC(=O)C=C1
1017	$C_8H_6O_4$	1,2-benzenedicarboxylic acid	OC(=O)c1ccccc1C(=O)O
10341	$C_4H_4O_2$	2 (5H)-furanone	C1OC(=O)C=C1
538757	$C_6H_8O_4$	2,4-dihydroxy-2,5-dimethyl-3(2H)furan-3-one	CC1=C(O)C(=O)C(O1)(C)O
574367	$C_5H_4O_3$	2H-pyran-2,6 (3H)-dione	O=C1CC=CC(=O)O1
545831	$C_4H_6O_3$	2-hydroxy-gamma-butyrolactone	O=C1OCCC1O
119838	$C_6H_8O_4$	2,3-dihydro-3,5-dihydroxy-6-methyl 4H-pyran-4-one	OC1COC(=C(C1=O)O)C
98431	$C_5H_8O_3$	(S)-(+)-2’,3’dideoxyribonolactone	OCC1CCC(=O)O1
541561	$C_6H_{10}O_5$	3-deoxy-D-mannoic lactone	OCC1OC(=O)C(CC1O)O
984	$C_{16}H_{32}O$	Hexadecanal	CCCCCCCCCCCCCCCC=O

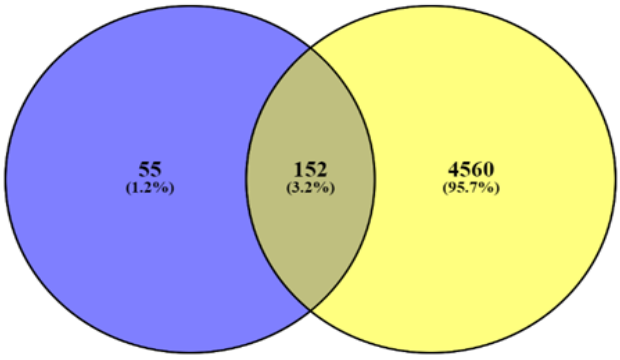

Fig. 1. Venn diagram of active compound targets of *Persicaria minor* (blue) and oxidative targets (yellow)

3.3 Network Construction and Topological Characterisation

The compound–target network created in Cytoscape (version 3.10.2) included 339 nodes (22 compound nodes and 117 target nodes) and 1,041 edges (Figure 2). The varied distribution of connections highlighted the multi-target and synergistic structure typical of herbal pharmacology. Topological metrics calculated using CytoNCA showed that Rhamnetin (DC = 38), Quercetin (DC = 37), Isorhamnetin (DC = 37), Eupatilin (DC = 36), and Kaempferol (DC = 35) had the highest degree centrality (DC) values, indicating that they are central hub compounds. These flavonoids dominate the interaction network of *P. minor*, reflecting their well-established redox-scavenging and signalling-modulating properties [20]. Mid-range compounds such as Citreorosein (DC = 28), Radiclonic acid (DC = 19), and Feruloyltyramine (DC = 17) contributed to secondary connectivity. In contrast, lower-degree nodes, Esculetin and Caffeic acid (DC = 11), represented more selective target interactions. This tiered connectivity pattern supports a hierarchical model of phytochemical synergy in which flavonoids serve as network anchors, supported by smaller phenolic molecules that fine-tune redox modulation [17]. Among the protein nodes, MMP9 (DC = 9), MMP2 (DC = 9), SYK (DC = 8), MMP3 (DC = 8), XDH (DC = 7), MMP13 (DC = 7), and NOX4 (DC = 6) emerged as hub targets with DC above the average of 4.312. Many of these proteins are directly involved in oxidative signalling, extracellular matrix remodelling, and inflammatory cascades. The dense connectivity between flavonoids and these enzymes supports the hypothesis that *P. minor* influences both antioxidant defence and cellular stress adaptation pathways.

3.4 Functional and Pathway Enrichment

To elucidate the biological relevance of the identified compound–target associations, functional enrichment analyses were performed using the ShinyGO platform across two annotation dimensions: KEGG pathways and Gene Ontology (GO) Biological Process (BP). Statistical significance was defined at $p < 0.05$ and $FDR < 0.05$ (Benjamini–Hochberg correction). The results reveal a multi-layered antioxidant mechanism of *Persicaria minor*, involving phosphorylation-dependent signal regulation, oxidative metabolism, and subcellular coordination of redox control (Figure 3a-b).

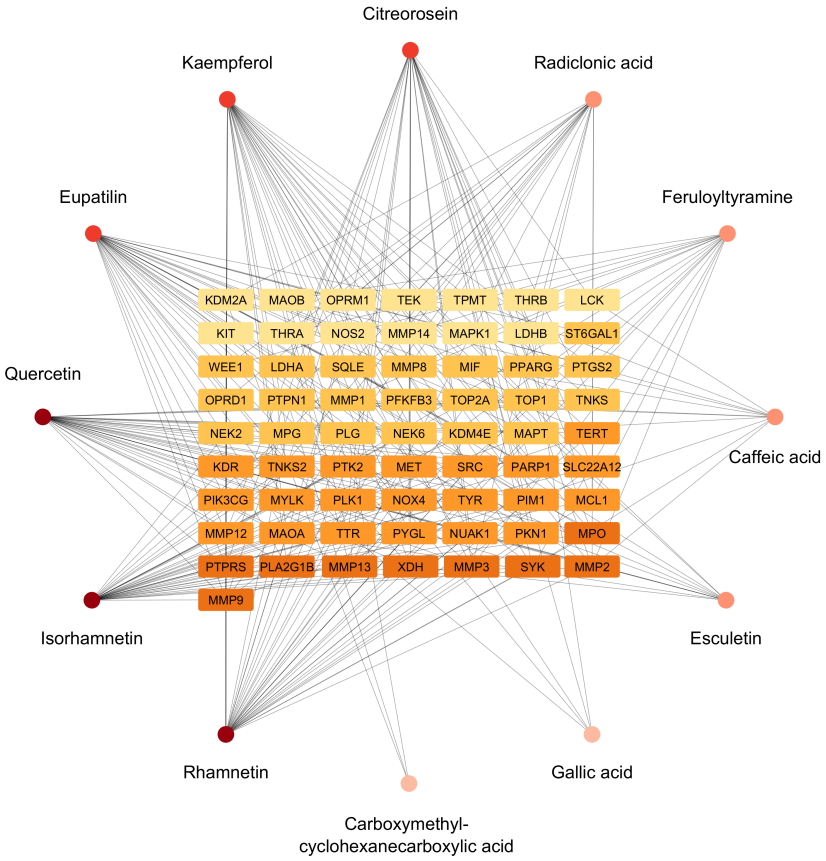

Fig 2. Compound-target network between the identified compounds of *Persicaria minor* and their predicted molecular targets. Round-shaped nodes stand for compounds of *P. minor*. Rectangular nodes represent the target genes. Colour ranking from darkest to lightest indicates the highest to the lowest degree

3.5.1 KEGG Pathway Enrichment and Target Mapping

The KEGG analysis identified 20 significantly enriched pathways, mainly involving redox-sensitive and cancer-related signalling networks (Figure 3a). The most enriched pathways were PI3K–AKT signalling (FDR = 1.47×10^{-4}; fold enrichment = 11.53), Proteoglycans in cancer (FDR = 1.47×10^{-4}; fold = 17.63), and Fluid shear stress and atherosclerosis (FDR = 1.74×10^{-4}; fold = 21.15). Key molecular mediators across these networks include KDR (VEGFR2), MET, SRC, PTK2 (FAK), and MMP family proteins (MMP2, MMP3, MMP9, MMP13), which are known to regulate oxidative signalling, matrix remodelling, and survival pathways. The co-occurrence of NOX4 and PIM1 within the Chemical carcinogenesis–reactive oxygen species pathway (hsa05208) directly links P. minor's activity to the modulation of ROS-producing enzymes. Notably, the PI3K–AKT pathway includes KDR, MCL1, MET, PIK3CG, PKN1, PTK2, and SYK, reflecting a complex phosphorylation network that governs redox homeostasis, angiogenesis, and apoptosis. Simultaneous enrichment in Focal adhesion (hsa04510), VEGF signalling (hsa04370), and IL-17 signalling (hsa04657) highlights the crosstalk between oxidative stress, inflammation, and cell adhesion. Enriched cancer-related pathways, such as transcriptional misregulation in cancer, Endocrine resistance, EGFR tyrosine kinase inhibitor resistance, and Bladder cancer, collectively suggest P. minor's potential to interfere with oncogenic ROS signalling and therapy resistance mechanisms via hub genes MET, SRC, and PTK2. Overall, these findings suggest

that P. minor bioactives modulate a central redox-regulatory axis that integrates the PI3K–AKT, VEGF, and HIF-1 pathways, thereby maintaining oxidative balance and counteracting pro-tumorigenic signalling.

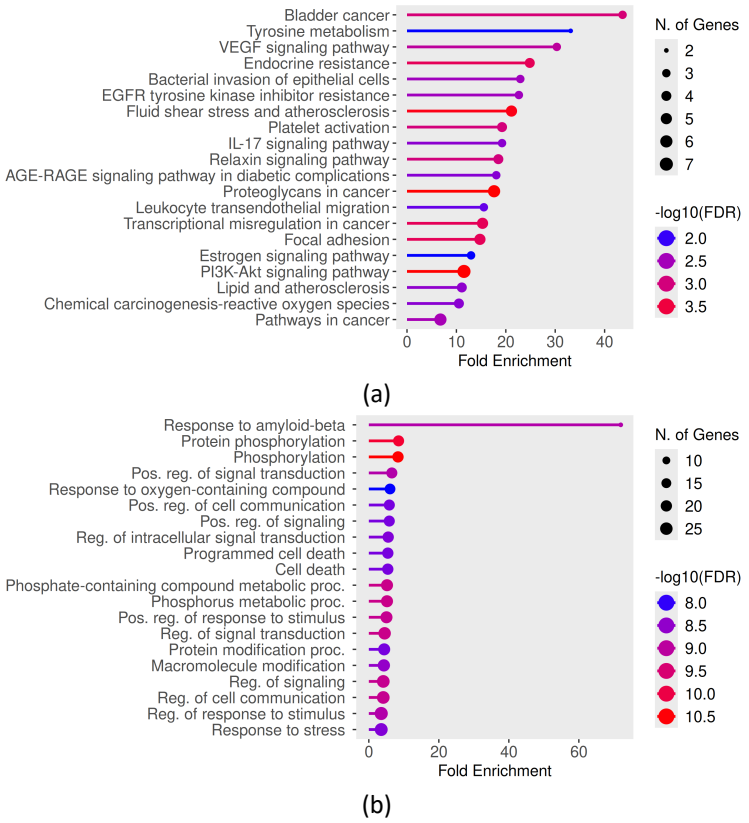

Fig. 3. Functional enrichment of hub targets of *Persicaria minor* (a) KEGG pathways, (b) GO Biological Process

3.5.2 GO Biological Process (BP) Enrichment

The GO Biological Process (BP) enrichment (Figure 3b) showed that the main targets of P. minor are mainly involved in phosphorylation-driven signalling, oxidative regulation, and stress adaptation. The most enriched terms—protein phosphorylation (FDR = 6.35×10^{-11}; fold enrichment = 8.51) and phosphorylation (FDR = 2.95×10^{-11}; fold enrichment = 8.33)—involve key kinases such as PIK3CG, PTK2, PLK1, NEK2, NEK6, SRC, and NOX4, confirming a phosphorylation-dependent mode of action. Processes such as positive regulation of signal transduction (FDR = 1.34×10^{-9}; fold = 6.58) and regulation of intracellular signal transduction (FDR = 4.30×10^{-9}; fold = 5.54) further suggest that these kinases operate within networks controlling oxidative response, apoptosis, and cell survival. Hub genes, such as PIK3CG, PTK2, MET, SYK, PARP1, and MCL1, highlight the coordination between redox control and pro-survival signalling through the PI3K–AKT and MAPK pathways. Oxidative stress–related processes, including responses to oxygen-containing compounds (FDR = 1.13×10^{-8}) and to stress (FDR = 4.20×10^{-9}), are highly enriched, involving NOX4, MPO, TYR, and several MMPs (2, 3, 9, 13). The enrichment of response to amyloid-beta (FDR = 1.35×10^{-9}; fold = 71.97) further indicates a protective function against oxidative and inflammatory cascades mediated by SYK, PARP1, and MMP family members. Terms related to apoptosis, such as programmed cell death (FDR = 5.09×10^{-9}; fold = 5.43), emphasise the involvement of MCL1, PTK2, PARP1, and SYK in redox-linked regulation of apoptosis. Overall, these results suggest that P. minor orchestrates a phosphorylation–

oxidative response-cell survival axis, reinforcing its role as a multi-target regulator of redox homeostasis and cellular resilience. The GO-BP enrichment complements the KEGG pathway crosstalk among PI3K–AKT, HIF-1, and VEGF pathways, outlining a coordinated antioxidant and cytoprotective response.

4. Discussion

This study systematically elucidates the antioxidant mechanisms of *Persicaria minor* through an integrated network pharmacology approach, combining phytochemical identification, ADME-based screening, and multi-dimensional enrichment analyses. The findings delineate a robust redox-modulatory framework in which *P. minor*'s flavonoids and phenolic derivatives coordinate phosphorylation-dependent signalling, oxidative defence, and apoptosis regulation through a multi-target network.

Among the 27 screened compounds, five flavonoids, isorhamnetin, quercetin, rhamnetin, eupatilin, and kaempferol, emerged as the dominant nodes within the compound–target network, exhibiting the highest degree centrality (DC = 35–38). Their connectivity to multiple redox-regulating enzymes and kinases underscores their system-wide pharmacological influence.

Isorhamnetin exhibited the highest topological prominence in the network, showing strong interactions with *NOX4*, *XDH*, *MMP2*, and *PTK2*. Its well-documented ability to attenuate ROS generation and modulate PI3K–AKT and MAPK pathways indicates a central role as a master regulator of oxidative signalling and apoptosis. Previous studies have reported that isorhamnetin suppresses *CA9* and *HIF-1α* activation, thereby reinforcing its potential as an intracellular redox stabiliser. Notably, Kong *et al.* [18] demonstrated that isorhamnetin-3-O-β-D-glucopyranoside enhances antioxidant enzyme activity and scavenges ROS in vitro. Complementing these findings, our network analysis predicts that isorhamnetin also targets *XDH* and *NOX4*, suggesting that it modulates redox homeostasis through the purine-catabolism and NADPH-oxidase axes. This dual-level regulation is consistent with recent reviews describing isorhamnetin as a versatile modulator of cellular redox signalling [19].

Quercetin, a structurally related flavonol, interacts with *SYK*, *MMP9*, and *PARP1*, which are targets centrally involved in oxidative DNA damage, inflammation, and extracellular matrix remodelling. Its predicted inhibition of NOX-derived ROS and NF-κB signalling is supported by extensive experimental evidence. Sul and Ra [20] demonstrated that quercetin effectively suppresses the NOX2/ROS/NF-κB axis in lipopolysaccharide-stimulated lung epithelial cells, thereby attenuating oxidative stress and pro-inflammatory cytokine production. Consistently, Lu *et al.* [21] demonstrated that quercetin activates the AMPK/SIRT1/NF-κB pathway, thereby mitigating methylglyoxal-induced inflammation through the restoration of redox balance and metabolic regulation. Furthermore, Baba *et al.* [22] demonstrated that quercetin directly targets Rac1 activation in glioma cells, leading to reduced ROS generation, cellular migration, and metastatic potential. Together, these studies consolidate quercetin's dual role as a redox-metabolic stabiliser and transcriptional regulator, capable of modulating oxidative and inflammatory cascades through Rac1–NOX–AMPK–NF-κB signalling. Within the *P. minor* network, quercetin thus emerges as a key bioactive compound that orchestrates anti-inflammatory, anti-migratory, and anti-apoptotic effects through the integrated regulation of NADPH-oxidase, AMPK/SIRT1, and NF-κB-dependent pathways.

Rhamnetin, with a degree centrality of 38, shares overlapping targets with quercetin but exhibits stronger predicted interactions with MCL1 and PTK2. These associations imply mitochondrial preservation through anti-apoptotic signalling and modulation of focal adhesion dynamics, consistent with its cytoprotective profile. Mechanistically, rhamnetin has been recognised as a

multifunctional flavonoid with potent anti-cancer, antioxidant, and anti-inflammatory activities. Abdel-Rasol et al. [23] highlighted its capacity to modulate apoptotic, angiogenic, and redox-sensitive pathways, positioning it as a promising therapeutic scaffold in oxidative stress–related malignancies. Supporting this, Yang et al. [24] demonstrated that rhamnetin suppresses bradykinin-induced MMP-9 expression and astrocyte migration by inhibiting ERK1/2 and NF-κB activation, confirming its direct regulation of inflammation-linked matrix signalling. Within the *P. minor* network, these experimentally supported mechanisms complement its predicted engagement with MCL1 and PTK2, suggesting that rhamnetin may stabilise mitochondrial integrity while attenuating redox-triggered apoptotic and migratory processes. These findings designate rhamnetin as a dual-acting antioxidant and focal adhesion modulator, capable of harmonising oxidative signalling and cytoskeletal homeostasis through the regulation of the MCL1–PTK2–MMP9 axis.

Eupatilin and kaempferol, two structurally related redox-active flavones, were identified as integral nodes within the *P. minor* network through their interactions with MMP2, MMP9, and SYK. Eupatilin's strong affinity for PTK2 and SRC indicates a regulatory role in suppressing oxidative stress-induced cell adhesion and migration. Supporting this, Lee et al. [25] demonstrated that eupatilin provokes mitochondrial dysfunction and ROS-driven apoptosis in colon cancer cells, thereby linking its cytotoxic activity to the control of oxidative signalling. These findings substantiate the present network prediction that eupatilin acts at the intersection of FAK/SRC-mediated adhesion and oxidative stress regulation. Conversely, kaempferol is predicted to reinforce antioxidant defence via Nrf2-dependent transcriptional activation. Haroon and Kang [26] further reported that kaempferol synergistically enhances cisplatin-induced apoptosis and cell-cycle arrest in colon cancer cells through modulation of oxidative stress pathways, confirming its capacity to amplify ROS-driven therapeutic responses. Within the *P. minor* network, eupatilin and kaempferol therefore function cooperatively: eupatilin limits oxidative injury and metastatic behaviour through PTK2/SRC-linked redox suppression, whereas kaempferol fortifies intracellular antioxidant resilience via Nrf2-mediated signalling, collectively contributing to the plant's integrated cytoprotective and anti-proliferative profile.

Beyond the core flavonoids, several secondary network contributors, notably feruloyltyramine, citreorosein, and radiclonic acid, serve as auxiliary regulators of *P. minor*'s redox network. Feruloyltyramine, a naturally occurring phenolic amide, demonstrated predicted interactions with *mTOR* and *BRAF*, suggesting its involvement in redox-sensitive growth and survival signalling. As reviewed by Evidente and Masi [27], cinnamoyltyramine-type alkylamides exhibit antioxidant, anti-inflammatory, and enzyme-modulatory properties, supporting their role as redox-interactive cofactors within polyphenolic systems. Similarly, Kumar *et al.* [28] highlighted phenolic amides as multifunctional phytochemicals that can regulate oxidative metabolism and enhance cellular stress tolerance. In contrast, citreorosein, an anthraquinone derivative, and radiclonic acid, a furanone compound, were both predicted to interact with *NOX4* and *XDH*, enzymes responsible for ROS generation in the NADPH-oxidase and purine-catabolism pathways. These associations imply the selective modulation of enzymatic ROS production, contributing to the maintenance of oxidative equilibrium. Collectively, these secondary metabolites reinforce the hierarchical phytochemical synergy of *P. minor*, wherein phenolic amides and quinone derivatives stabilise the oxidative–antioxidant balance through cooperative regulation of mTOR, BRAF, NOX4, and XDH signalling axes.

Functional enrichment further revealed convergence upon phosphorylation-regulated networks, particularly PI3K–AKT, MAPK, HIF-1, and VEGF signalling. These pathways integrate oxidative cues with metabolic and survival responses, as evidenced by the central roles of *PIK3CG, PTK2, MET, PARP1,* and *MCL1*. The enrichment of protein phosphorylation (FDR = 6.35×10^{-11}) and response to oxygen-containing compounds (FDR = 1.13×10^{-8}) substantiates phosphorylation-dependent ROS

control as a defining mechanism of *P. minor* bioactivity. The simultaneous activation of VEGF and HIF-1 pathways implies an adaptive cytoprotective strategy, enhancing angiogenic recovery and hypoxia resilience.

GO enrichment for response to stress and programmed cell death (FDR ≈ 5×10^{-9}) indicates a finely tuned redox-linked apoptotic regulation, mediated by *MCL1, PTK2, PARP1,* and *SYK*. Remarkably, the enrichment of response to amyloid-β (FDR = 1.35×10^{-9}; fold = 71.97), driven by *SYK, PARP1,* and *MMPs*, extends the antioxidant implications toward neuroprotective potential, suggesting attenuation of oxidative–inflammatory cascades in neurodegenerative contexts.

These findings support an integrative mechanistic model in which *P. minor* bioactives act as redox regulators targeting phosphorylation cascades, ROS-producing enzymes, and apoptotic mediators. The flavonoid nucleus (*isorhamnetin–quercetin–rhamnetin–kaempferol–eupatilin*) serves as the primary regulatory core, complemented by phenolic amides and anthraquinones as secondary modulators that enhance systemic redox resilience. This hierarchical multi-target orchestration reflects the emerging pharmacological paradigm that prioritises network and pathway modulation over single-target inhibition in complex disease management.

Finally, by connecting molecular interactions with cellular processes, this study positions *Persicaria minor* as a systems-level antioxidant with translational potential in disorders characterised by oxidative imbalance, such as cancer, cardiovascular dysfunction, and neurodegeneration. Its modulation of *NOX4, MMPs, PTK2, PARP1,* and *MCL1* highlights concurrent anti-inflammatory, anti-metastatic, and anti-apoptotic properties. Future investigations integrating molecular docking, dynamics simulations, and experimental validation, especially targeting AKT phosphorylation, Nrf2 activation, and ROS quantification, will be essential to confirm the predicted interactions and define compound-specific contributions. Moreover, multi-omics approaches encompassing metabolomics and proteomics will be invaluable for mapping the dynamic redox networks orchestrated by *P. minor* in cellular systems.

4. Conclusion

Network pharmacology analysis identified isorhamnetin, quercetin, rhamnetin, eupatilin, kaempferol, feruloyltyramine, and radiclonic acid as key bioactives of *P. minor,* orchestrating a phosphorylation-dependent antioxidant mechanism. Through coordinated modulation of PI3K–AKT, MAPK, and VEGF pathways and regulation of redox-sensitive targets (NOX4, MMPs, PTK2, PARP1, MCL1), *P. minor* maintains oxidative balance and supports cell survival. These findings present *P. minor* as a promising multi-target botanical agent for mitigating oxidative stress–related diseases and establish a molecular framework for subsequent experimental validation.

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Conflict of interest

The authors declare that thereare no conflicts of interest.

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