Journal of Advanced Research in Applied Sciences and Engineering Technology

Journal homepage:
https://semarakilmu.com.my/journals/index.php/applied_sciences_eng_tech/index
ISSN: 2462-1943

In Silico Prioritisation of *Persicaria minor* Phytochemicals and Predicted Cancer-Associated Molecular Targets

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ARTICLE INFO

Article history:
Received 26 July 2026
Received in revised form 30 September 2026
Accepted 30 September 2026
Available online 9 October 2026

Keywords:
Persicaria minor; cancer-associated targets; network pharmacology; phytochemicals; target prediction

ABSTRACT

Persicaria minor (Huds.) Opiz, an aromatic herb in the Polygonaceae family, contains phenolic acids, flavonoids and other metabolites associated with diverse biological properties. This study aimed to use network pharmacology to prioritise reported *P. minor* constituents and predict cancer-associated molecular targets. A total of 143 compound records were compiled from published literature and public databases; after duplicate removal, 131 unique compounds were screened using SwissADME for drug-likeness and pharmacokinetic properties. Of 27 prioritised compounds, 22 generated SwissTargetPrediction outputs, yielding 207 non-duplicate predicted human targets. Intersection with GeneCards-derived cancer-associated genes identified 109 common targets. The resulting cancer-focused compound–target network comprised 17 compounds, 109 target nodes and 491 predicted associations. Isorhamnetin, quercetin, kaempferol, rhamnetin and eupatilin showed the highest compound connectivity. Protein–protein interaction analysis of the 109 common targets generated a network of 109 proteins and 1,137 associations, with AKT1, CASP3, BCL2, ESR1, HSP90AA1, EGFR, PTGS2, SRC and PPARG among the most highly connected proteins. KEGG enrichment identified multiple cancer-associated pathways, with PI3K–AKT signalling among the most significantly enriched. These findings provide a structured framework for prioritising candidate phytochemicals, proteins and signalling pathways for further investigation. Chemical confirmation and experimental validation are required before mechanistic or therapeutic inferences can be drawn.

1. Introduction

Cancer remains a major global health burden, with an estimated 20 million new cases and 9.7 million deaths worldwide in 2022 [1]. Natural products and their derivatives have contributed substantially to drug discovery, including anticancer drug development, and continue to provide chemically diverse scaffolds for pharmacological investigation [2,3]. Computational approaches increasingly enable systematic prioritisation of natural-product constituents and their potential

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molecular targets. Such predictions are hypothesis-generating and require chemical and experimental validation before mechanistic or therapeutic conclusions can be drawn.

Phytochemical investigations across Persicaria and Polygonum have identified diverse secondary metabolites, including flavonoids, sesquiterpenoids and other phenolic compounds [4]. Persicaria minor (Huds.) Opiz, commonly known as kesum, is an aromatic herb used in food preparation and traditional medicine in Southeast Asia [5,6]. Studies on P. minor have also reported antioxidant, antimicrobial, anti-inflammatory, and cytotoxic activities [5,6]. Methoxylated flavonoids have been isolated from P. minor [7], while gallic acid, rutin, coumaric acid and quercetin were detected chromatographically in a fraction of the plant [8]. More recently, polygonumins B, C and D were isolated from P. minor and evaluated using biochemical assays and molecular docking [9]. Across these studies, differences in plant material, extraction and fractionation procedures, and analytical methods limit direct comparison of reported phytochemical profiles [7–9].

Network pharmacology provides a framework for integrating phytochemicals with predicted protein targets and disease-associated genes [10,11]. Protein–protein interaction analysis and pathway enrichment can further identify highly connected proteins and over-represented biological processes. However, integrated analyses linking a curated P. minor phytochemical set with cancer-associated target prioritisation, PPI topology, and pathway-level interpretation remain limited. Addressing this gap may provide a structured basis for prioritising candidate compounds, proteins and signalling pathways for subsequent chemical and experimental validation. Therefore, this study sought to: (i) curate and screen reported P. minor compounds; (ii) predict human protein targets and construct a cancer-focused compound–target network; (iii) analyse PPI network topology; and (iv) identify enriched cancer-associated pathways and visualise prioritised signalling modules.

2. Methodology

2.1 Phytochemical Data Collection and Structure Curation

Studies reporting P. minor and its synonym Polygonum minus were searched in Scopus, PubMed, ScienceDirect, IMPPAT, KNApSAcK, TCMSP and Dr Duke's Phytochemical and Ethnobotanical Database using the terms “Persicaria minor”, “Polygonum minus”, “phytochemical” and “compound”, with Boolean combinations as appropriate. Compound names were normalised, duplicates were removed, and canonical SMILES strings, molecular formulae and molecular weights were verified using PubChem. Compound records lacking a verifiable chemical structure were excluded. Database records were treated as evidence of reported association with P. minor, rather than confirmation of occurrence in a defined extract. Table 1 summarises the databases and computational tools used for compound curation, pharmacokinetic screening, target prediction and subsequent network analyses.

2.2 Drug-Likeness and Pharmacokinetic Screening

Canonical SMILES strings were submitted to SwissADME to predict physicochemical properties, drug-likeness, and selected pharmacokinetic attributes [12]. Duplicate structures were removed. Initial screening applied a bioavailability score ≥ 0.55 together with Lipinski-rule assessment, reducing the dataset from 131 to 128 compounds. Compounds predicted to have high gastrointestinal absorption and no blood–brain barrier permeation were subsequently prioritised, resulting in 27 compounds for target prediction. These criteria were used for computational prioritisation and were not considered evidence of biological activity, safety or clinical bioavailability [12,13].

Table 1

Databases and computational tools used in the study

Resource	Purpose	Accessed information
Scopus, PubMed and ScienceDirect	Literature search	Reported *P. minor* constituents and biological activities
IMPPAT, KNApSAcK, TCMSP and Dr. Duke's Phytochemical and Ethnobotanical Database	Phytochemical retrieval	Species–compound records
PubChem	Structure curation	Canonical SMILES, molecular formulae and molecular weights
SwissADME	In silico screening	Physicochemical properties, drug-likeness and pharmacokinetic predictions
SwissTargetPrediction	Target prediction	Predicted human protein targets
GeneCards	Disease–gene retrieval	Cancer-associated genes and relevance scores
Cytoscape 3.10.3 / NetworkAnalyzer	Network construction and topological analysis	Network visualisation, degree, betweenness centrality and closeness centrality
STRING v12.0	Protein–protein association analysis	Protein association network and network-level statistics
ShinyGO with KEGG annotations	Pathway enrichment	Enriched KEGG pathways, FDR, mapped gene count and fold enrichment
Pathview	Pathway-level visualisation	Mapping of input target genes onto the selected KEGG pathway

2.3 Target Prediction and Cancer-Associated Genes

The 27 prioritised compounds were submitted to SwissTargetPrediction using Homo sapiens as the target organism [14]. Predictions with probability > 0 were retained. Of the 27 compounds, 22 generated target predictions, yielding 207 non-duplicate predicted human targets after duplicate target removal. Cancer-associated genes were retrieved from GeneCards using the terms "cancer", "tumour" and "neoplasm", with a relevance score ≥ 1 [15]. The 207 predicted human targets were intersected with the GeneCards-derived cancer-associated gene set, yielding 109 common cancer-associated predicted targets. These targets were retained for subsequent compound–target network, PPI and pathway-enrichment analyses.

2.4 Compound–Target Network Construction and Topology

The cancer-focused compound–target network was constructed in Cytoscape 3.10.3 by retaining predicted associations between the prioritised compounds and the 109 common cancer-associated targets [16]. Nodes represented compounds or predicted targets, whereas edges represented predicted compound–target associations. Compounds with no associations with the common cancer-associated target set were excluded from the final network. Node degree was calculated using Cytoscape NetworkAnalyzer and used as the primary criterion for ranking compounds because it represents the number of predicted target associations within the network. Degree was interpreted solely as a measure of network connectivity, not as evidence of binding affinity, potency, efficacy, or other pharmacological activity.

2.5 Protein–Protein Interaction Analysis

The 109 common cancer-associated predicted targets were submitted to STRING v12.0 using Homo sapiens as the organism [17]. Protein–protein associations were retrieved using a minimum required interaction score of 0.400 (medium confidence), with no additional interactors. STRING-

derived network statistics, including the number of nodes and associations, average node degree, average local clustering coefficient, expected number of associations and PPI enrichment p-value, were recorded. The resulting PPI network was imported into Cytoscape 3.10.3 [16], where NetworkAnalyzer was used to calculate node-level degree, betweenness centrality and closeness centrality. Degree represents direct connectivity, betweenness reflects network-bridging position, and closeness represents the relative proximity of a node to other nodes in the network.

2.6 KEGG Pathway Enrichment and Pathway Mapping

Functional enrichment analysis was performed in ShinyGO using the 109 common cancer-associated predicted targets and KEGG pathway annotations [18]. The tool-reported false discovery rate (FDR), mapped gene count and fold enrichment were used to characterise the enriched pathways. PI3K–AKT signalling was subsequently selected for pathway-level visualisation, and the same 109-target set was mapped onto the KEGG PI3K–AKT signalling pathway using Pathview [19]. Highlighted pathway nodes indicate representation of genes from the analysed target set and do not indicate upregulation, downregulation, activation or inhibition.

3. Results

3.1 Compound Curation, Screening and Target Prediction

Database and literature searches identified 143 compound records associated with P. minor. Removal of 12 duplicate records yielded 131 non-redundant compounds. Initial bioavailability score/Lipinski-rule screening reduced this set to 128 compounds, followed by prioritisation based on high predicted gastrointestinal absorption and absence of predicted blood–brain barrier penetration, yielding 27 compounds. Of these, 22 generated SwissTargetPrediction outputs, yielding 207 non-duplicate predicted human targets. Intersection with the GeneCards-derived cancer-associated gene set identified 109 common cancer-associated predicted targets (Table 2). These filtering steps reduced the chemical search space for subsequent computational analysis but do not imply that excluded compounds lack biological activity or that retained compounds are suitable for clinical use. Drug-likeness and pharmacokinetic predictions are prioritisation criteria rather than direct evidence of biological activity, systemic exposure, safety or therapeutic efficacy [12,13].

Table 2
Sequential compound curation, screening and target prediction

Stage	Screening/processing step	Number retained
1	Initial *P. minor* compound records identified	143 compounds
2	After removal of 12 duplicate records	131 compounds
3	After bioavailability score/Lipinski-rule screening	128 compounds
4	After prioritisation for high gastrointestinal absorption and absence of predicted blood–brain barrier penetration	27 compounds
5	Compounds generating SwissTargetPrediction outputs	22 compounds
6	Non-duplicate predicted human targets	207 targets
7	Common cancer-associated predicted targets after GeneCards intersection	109 targets

3.2 Cancer–Focused Compound-Target Network

The cancer-focused network comprised 17 compound nodes, 109 target nodes and 491 predicted compound–target associations (Figure 1). Isorhamnetin showed the highest compound degree (63), followed by quercetin (62), kaempferol and rhamnetin (60), eupatilin (57), citreorosein (44), feruloyltyramine (34), radiclonic acid (30), esculetin (26) and caffeic acid (21). These highly connected compounds showed broad predicted target coverage within the cancer-associated target set. Degree represents the number of predicted target associations within the analysed network and does not indicate greater binding affinity, potency or anticancer efficacy.

Experimental studies have reported anticancer activity of isorhamnetin in doxorubicin-resistant breast cancer cells [20], quercetin in HER2-overexpressing breast cancer cells [21] and kaempferol in breast cancer models [22]. These findings provide independent biological context for prioritising these compounds but do not validate the individual compound–target associations predicted in the present study.

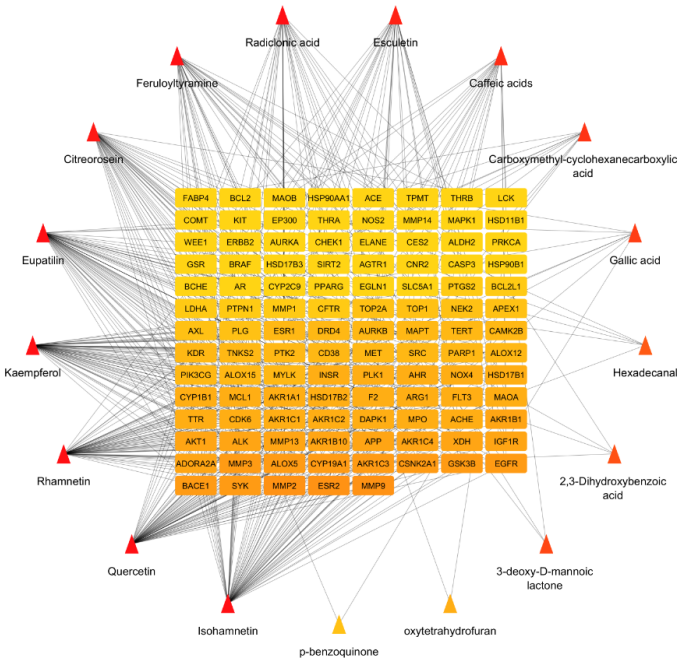


Fig. 1. Cancer-focused compound–target network comprising 17 compound nodes, 109 target nodes and 491 predicted compound–target associations. Triangular nodes represent compounds and rectangular nodes represent predicted cancer-associated targets. Node colour reflects degree. Each edge represents a predicted compound–target association and does not establish direct molecular binding

3.3 Protein–Protein Interaction Network Topology

STRING analysis of the 109 common cancer-associated predicted targets generated a network comprising 109 protein nodes and 1,137 protein–protein associations, with an average node degree of 20.9 and an average local clustering coefficient of 0.62. The network contained 1,137 associations compared with 455 expected, with a PPI enrichment $p < 1.0 \times 10^{-16}$. AKT1 showed the highest degree (72), followed by CASP3 (64), BCL2 (63), ESR1 (61), HSP90AA1 (60), EGFR (59), PTGS2 and SRC (54 each), and PPARG (52) (Figure 2). The complete STRING-derived association network is shown in Figure 3.

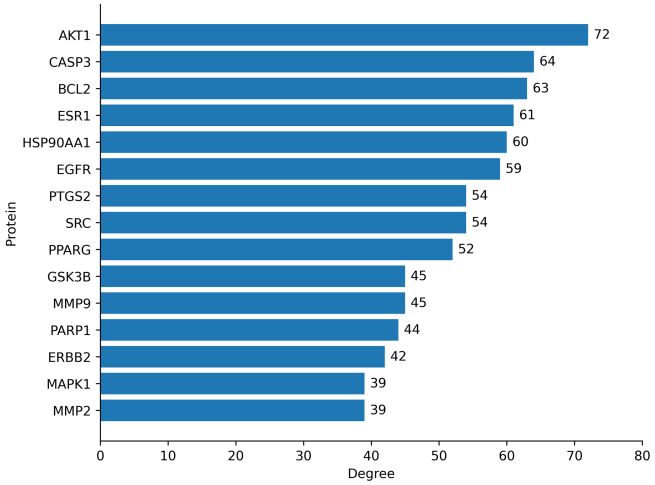


Fig. 2. Top 15 proteins ranked by degree in the STRING-derived PPI network constructed from the 109 common cancer-associated predicted targets. Degree represents the number of direct protein associations of each node within the analysed network

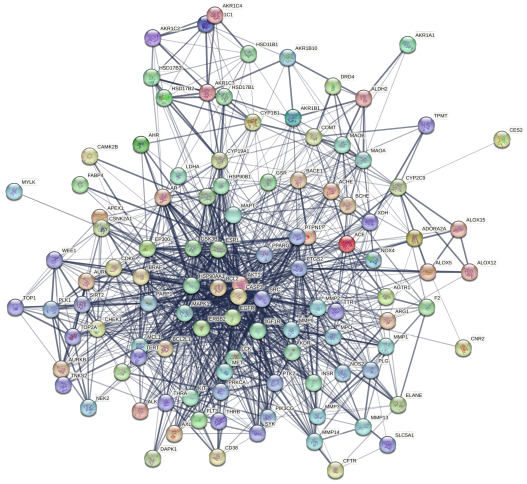


Fig. 3. STRING-derived protein–protein association network constructed from the 109 common cancer-associated predicted targets. Nodes represent proteins and edges represent protein–protein associations retrieved using a minimum required interaction score of 0.400, with no additional interactors

Centrality rankings varied across the different topological measures. AKT1 ranked first in degree (72), betweenness centrality (0.094) and closeness centrality (0.735). ESR1 (0.082), HSP90AA1 (0.072), SRC (0.056) and PTGS2 (0.056) also showed high betweenness centrality, whereas CASP3 (0.697), BCL2 and ESR1 (0.692 each), HSP90AA1 (0.688) and EGFR (0.675) showed high closeness centrality (Table 3). Degree reflects direct connectivity, whereas betweenness and closeness centralities describe network-bridging position and relative proximity to other proteins, respectively. Proteins ranking highly across these complementary measures were considered candidate network hubs for further investigation rather than experimentally validated anticancer targets.

Table 3
Centrality characteristics of highly connected proteins in the PPI network

Protein	Degree	Betweenness centrality	Closeness centrality
AKT1	72	0.094	0.735
CASP3	64	0.047	0.697
BCL2	63	0.041	0.692
ESR1	61	0.082	0.692
HSP90AA1	60	0.072	0.688
EGFR	59	0.055	0.675
PTGS2	54	0.056	0.667
SRC	54	0.056	0.647
PPARG	52	0.049	0.655

3.4 KEGG Pathway Enrichment

KEGG enrichment analysis of the 109 common cancer-associated predicted targets identified 20 significantly over-represented pathways (Figure 4). Pathways in cancer showed the greatest statistical significance, comprising 35 mapped genes, with a fold enrichment of 13.86 and an FDR of 3.98×10^{-28}. EGFR tyrosine kinase inhibitor resistance comprised 14 genes with a fold enrichment of 37.20 (FDR = 1.50×10^{-16}), whereas PI3K–AKT signalling comprised 21 genes with a fold enrichment of 12.45 (FDR = 1.58×10^{-15}). Other prominent terms included prostate cancer, endocrine resistance, proteoglycans in cancer, steroid hormone biosynthesis, chemical carcinogenesis–reactive oxygen species and HIF-1 signalling. Focal adhesion, ErbB signalling and oestrogen signalling were also significantly enriched.

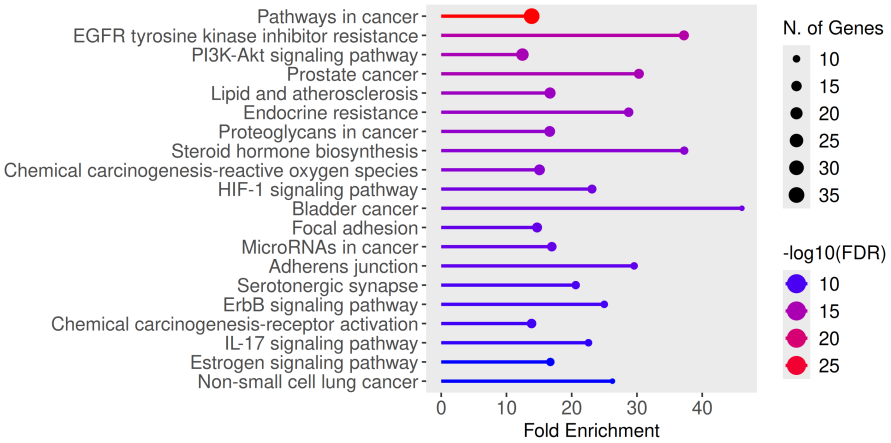


Fig. 4. KEGG pathway enrichment of the 109 common cancer-associated predicted targets. Point size represents the number of mapped genes, colour represents $-\log_{10}$(FDR), and the horizontal axis represents fold enrichment

The enrichment profile reflects a broad pan-cancer target space rather than a tumour-type-specific signature. Disease-specific terms such as prostate cancer, bladder cancer and non-small cell lung cancer therefore reflect molecular components shared across tumour-associated signalling programmes rather than evidence of selective activity of P. minor against those cancer types. This interpretation is consistent with shared hallmark processes across diverse human cancers [23]. Enrichment of endocrine resistance and oestrogen signalling similarly reflects hormone-regulated and growth-factor-associated signalling components; crosstalk between oestrogen-receptor and growth-factor signalling, including PI3K/mTOR and MAPK-related pathways, contributes to endocrine resistance [24]. Enrichment of chemical carcinogenesis–reactive oxygen species further indicates

representation of redox-related processes. Oxidative stress can influence cancer-associated transcription, inflammation, cell growth and survival [25]. Collectively, these findings identify cancer-associated signalling, hormone-related regulation and redox processes as prominent computational themes but do not establish pathway activity or selective anticancer effects.

3.5 PI3K–AKT Pathway Mapping and Integrated Interpretation

PI3K–AKT signalling was selected for pathway-level visualisation because it was among the most significantly enriched pathways, comprising 21 genes from the 109-target set (fold enrichment = 12.45; FDR = 1.58×10^{-15}). Pathview mapping showed representation across receptor-associated signalling and downstream growth, survival and cell-cycle regulatory components, including EGFR, ERBB2, AKT1, GSK3B, HSP90AA1/HSP90B1, PTK2, PRKCA, MAPK1, BCL2, BCL2L1 and MCL1 (Figure 5). The highlighted nodes indicate pathway components represented by genes in the analysed target set and do not provide evidence of pathway activation, inhibition or differential expression.

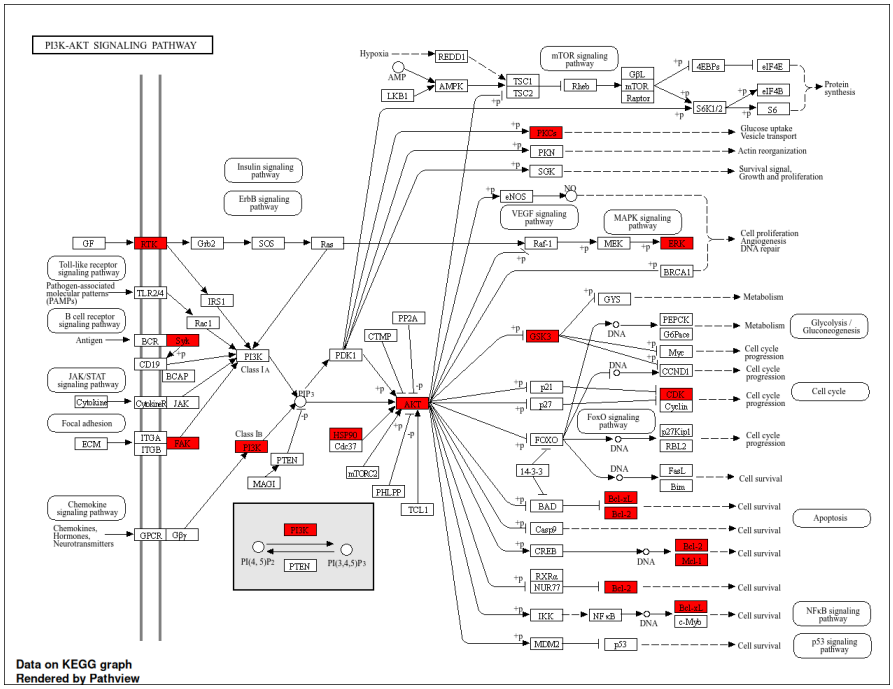


Fig. 5. Pathview mapping of the 109 common cancer-associated predicted targets onto the KEGG PI3K–AKT signalling pathway. Highlighted nodes represent pathway components mapped from the analysed target set; highlighting denotes pathway membership only and does not indicate activation, inhibition or differential expression

The strongest integrated pattern was the convergence of PPI connectivity and pathway enrichment around AKT1- and growth-factor-associated signalling. AKT1 ranked highest across all three PPI centrality measures, while EGFR, ESR1, HSP90AA1 and SRC were also among the highly connected proteins. This network topology was consistent with the enrichment of PI3K–AKT signalling and related pathways, including EGFR tyrosine kinase inhibitor resistance, endocrine resistance, ErbB signalling and oestrogen signalling. Receptor tyrosine kinases, including members of the EGFR family, engage interconnected downstream signalling networks involved in cancer-cell proliferation and survival, with PI3K–AKT representing a major downstream signalling axis [26]. PI3K–AKT signalling regulates fundamental cellular processes including growth, survival and metabolism [27]. The convergence of PPI topology, pathway enrichment and Pathview mapping therefore

provides a rational basis for prioritising this signalling context within the broader pan-cancer target space for experimental investigation. However, these computational findings do not demonstrate pathway activation or inhibition, nor do they establish that individual P. minor constituents directly modulate the mapped proteins.

3.6 Strengths, Limitations and Validation Priorities

A strength of the present study is its integration of compound prioritisation, compound–target network topology, PPI analysis using complementary centrality measures, pathway enrichment, and pathway-level visualisation within a single analytical framework. Nevertheless, several limitations warrant consideration. The compound library was assembled from published literature and phytochemical databases rather than from chemical profiling of a defined and authenticated P. minor extract. Consequently, reported records may be affected by differences in nomenclature, database annotation and historical identification, and the presence of individual compounds in the material relevant to this study cannot be assumed. In addition, the SwissADME-based prioritisation was intended to reduce the computational search space and may have excluded compounds with potentially relevant biological activity despite less favourable predicted pharmacokinetic properties [12].

SwissTargetPrediction infers potential targets from chemical similarity to compounds with known bioactivities [14]. Predictions may therefore include false-positive associations or miss biologically relevant targets. Retaining predictions with probability > 0 broadened target coverage but also included lower-confidence predictions; accordingly, the predicted compound–target associations remain hypothesis-generating rather than evidence of direct molecular interaction. The broad cancer-associated GeneCards query also limits tumour-type specificity, and the resulting 109-target set is therefore more appropriately interpreted as a pan-cancer target space than as a molecular signature of a single malignancy. PPI topology depends on the submitted proteins and the STRING interaction-confidence threshold [17], while pathway over-representation identifies statistical enrichment but does not establish pathway activation, inhibition or causal regulation [18].

A staged validation strategy would begin with chemical confirmation of prioritised constituents in a P. minor extract prepared under defined conditions, using chromatographic and mass-spectrometric approaches and, where feasible, authentic reference standards [28]. Confirmed compounds could then be evaluated for biological activity and selectivity in relevant cancer and non-malignant cellular models. Target-engagement assays could subsequently assess whether selected compounds engage high-priority proteins, followed by functional-perturbation studies to determine whether such engagement produces corresponding biological effects [29]. Finally, integrating cancer-type-specific transcriptomic and proteomic datasets could refine pan-cancer hypotheses by placing prioritised targets and pathways within more disease-relevant molecular contexts [30].

4. Conclusions

The cancer-focused compound–target network comprised 17 P. minor compounds, 109 common cancer-associated predicted targets and 491 predicted compound–target associations derived from 207 non-redundant predicted human targets. Isorhamnetin, quercetin, kaempferol, rhamnetin and eupatilin showed the highest compound connectivity. STRING analysis of the 109 common targets generated a PPI network comprising 109 proteins and 1,137 protein–protein associations, with AKT1, CASP3, BCL2, ESR1, HSP90AA1, EGFR, PTGS2, SRC and PPARG among the most highly connected proteins. KEGG enrichment identified multiple cancer-associated pathways, including PI3K–AKT

signalling, EGFR tyrosine kinase inhibitor resistance, endocrine resistance, HIF-1 signalling, focal adhesion, ErbB signalling, oestrogen signalling and chemical carcinogenesis–reactive oxygen species. PI3K–AKT signalling contained 21 mapped genes and provided a prominent pathway-level context for integrating the PPI and enrichment findings.

The compound–target network, PPI topology and pathway enrichment provide a structured pan-cancer framework for prioritising candidate compounds, proteins and signalling contexts for experimental investigation. However, these computational analyses do not confirm the occurrence of the prioritised compounds in a defined P. minor extract, demonstrate direct modulation of the predicted targets or establish anticancer efficacy. Chemical confirmation of prioritised constituents, target-focused experimental validation and cancer-relevant biological evaluation are therefore required before specific mechanistic or therapeutic conclusions can be drawn.

Acknowledgement
The authors acknowledge the Faculty of Pharmacy, Universiti Teknologi MARA, Malaysia, for institutional support.

Author Contributions
Sharifah Nur Alia Syed Mustafa: investigation, data curation, formal analysis, visualisation and writing - original draft. Noor Jannah Yob: conceptualisation, methodology, supervision, validation and writing - review and editing. Both authors approved the final manuscript.

Conflict of Interest
The authors declare no conflict of interest.

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