

Original Research

In Silico Exploration of the Angiogenic Potential of Theophylline as a Drug Repurposing Candidate through Network Pharmacology

Theodorus Rexa Handoyo^{1*}, Cherry Vanesa¹

¹Faculty of Pharmacy, Universitas 17 Agustus 1945 Jakarta, Jakarta Utara, Indonesia, 14350

*E-mail: theodorus.rexa@uta45jakarta.ac.id

Abstrak

Theophylline merupakan obat golongan metilxantin yang telah lama digunakan dalam pengobatan gangguan pernapasan, terutama asma dan penyakit paru obstruktif kronis. Selain aktivitas bronkodilatormya, theophylline memiliki profil farmakologis yang luas sehingga berpotensi memiliki aktivitas biologis lain di luar penggunaan konvensional. Penelitian ini bertujuan mengeksplorasi potensi theophylline sebagai kandidat drug repurposing yang berkaitan dengan angiogenesis menggunakan pendekatan network pharmacology. Target molekuler potensial theophylline diperoleh dari SwissTargetPrediction, sedangkan gen yang berhubungan dengan angiogenesis diperoleh dari GeneCards dengan kriteria Relevance Score >50. Gen yang beririsan antara kedua dataset kemudian dianalisis menggunakan protein-protein interaction (PPI), Cytoscape, dan CytoHubba dengan metode Maximal Clique Centrality (MCC). Analisis Gene Ontology (GO) dan Kyoto Encyclopedia of Genes and Genomes (KEGG) dilakukan untuk mengidentifikasi fungsi biologis dan jalur pensinyalan yang terkait. Hasil analisis mengidentifikasi enam target yang beririsan, yaitu KDR, EPHB4, SRC, TYMP, JAK2, dan PDE3B. Analisis PPI menunjukkan bahwa EPHB4, SRC, KDR, JAK2, dan PDE3B membentuk jaringan interaksi yang saling terhubung, sedangkan SRC dan JAK2 merupakan node dengan peringkat MCC tertinggi. Analisis GO menunjukkan keterkaitan dengan aktivitas tirosin kinase, aktivitas reseptor tirosin kinase transmembran, aktivitas reseptor vascular endothelial growth factor, serta regulasi pensinyalan PI3K/AKT. Analisis KEGG mengidentifikasi jalur VEGF signaling sebagai salah satu jalur yang diperkaya. Secara keseluruhan, hasil ini menunjukkan adanya hubungan molekuler potensial antara theophylline dan mekanisme yang berkaitan dengan angiogenesis, sehingga mendukung eksplorasi lebih lanjut theophylline sebagai kandidat drug repurposing. Namun, penelitian ini sepenuhnya berbasis komputasi dan bersifat hipotesis-generating, sehingga temuan yang diperoleh belum dapat dianggap sebagai bukti aktivitas angiogenik atau efektivitas terapeutik. Validasi melalui penelitian in vitro dan in vivo diperlukan untuk mengonfirmasi temuan tersebut.

Kata kunci: theophylline; angiogenesis; drug repurposing; network pharmacology; protein-protein interaction.

Abstract

Theophylline is a methylxanthine drug that has been widely used in the management of respiratory disorders, particularly asthma and chronic obstructive pulmonary disease. In addition to its bronchodilator activity, theophylline exhibits a broad pharmacological profile, suggesting that it may possess biological activities beyond its conventional therapeutic applications. This study aimed to explore the potential of theophylline as a drug repurposing candidate associated with angiogenesis using a network pharmacology approach. Potential molecular targets of theophylline were obtained from SwissTargetPrediction, while angiogenesis-associated genes were retrieved from GeneCards using a Relevance Score threshold of >50. Overlapping genes between the two datasets were subsequently analyzed using protein-protein interaction (PPI) analysis, Cytoscape, and CytoHubba with the Maximal Clique Centrality (MCC) method. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed to identify the biological functions and signaling pathways associated with the overlapping targets. Six overlapping targets were identified, namely KDR, EPHB4, SRC, TYMP, JAK2, and PDE3B. PPI analysis demonstrated that EPHB4, SRC, KDR, JAK2, and PDE3B formed a connected interaction network, while SRC and JAK2 showed the highest MCC rankings. GO analysis indicated associations with protein tyrosine kinase activity, transmembrane receptor protein tyrosine kinase activity, vascular endothelial growth factor receptor activity, and

regulation of PI3K/AKT signaling. KEGG analysis identified the VEGF signaling pathway among the enriched pathways. Overall, these findings indicate a potential molecular association between theophylline and angiogenesis-related mechanisms, supporting further investigation of theophylline as a drug repurposing candidate. However, this study is entirely computational and should be considered hypothesis-generating rather than evidence of angiogenic activity or therapeutic efficacy. Further in vitro and in vivo studies are required to validate the identified molecular associations and biological mechanisms.

Keywords: *theophylline; angiogenesis; drug repurposing; network pharmacology; protein-protein interaction.*

INTRODUCTION

Theophylline is a methylxanthine drug that has been used for decades in the management of respiratory disorders, particularly asthma and chronic obstructive pulmonary disease (COPD) (1). The drug has traditionally been recognized for its bronchodilator activity and has been used to improve airflow in patients with obstructive airway diseases. Pharmacologically, theophylline has a broad range of molecular actions, including inhibition of phosphodiesterase enzymes and antagonism of adenosine receptors (2). In addition to its bronchodilator effects, theophylline has also been associated with various immunomodulatory and anti-inflammatory activities. These diverse pharmacological properties indicate that the biological effects of theophylline may extend beyond its conventional respiratory applications (3).

The broad pharmacological profile of theophylline provides an opportunity to investigate whether this established drug may possess additional therapeutic applications beyond its primary indications. Drug repurposing refers to the investigation of an existing drug for a new therapeutic indication. This strategy provides an alternative approach to conventional drug discovery by utilizing compounds with established pharmacological characteristics as starting points for exploring new therapeutic applications (4). Identifying additional biological activities of existing drugs may therefore provide a rational basis for generating new therapeutic hypotheses (5).

The investigation of potential new applications for drugs with multiple molecular interactions requires an approach capable of examining several targets and biological pathways simultaneously (6). Network pharmacology provides a systems-level framework for integrating drug-target relationships, protein-protein interactions, biological processes, and signaling pathways (7,8). Rather than focusing on a single predetermined molecular target, network pharmacology enables the relationships between a drug and a broader biological network to be systematically investigated. This approach can therefore be applied to identify potential molecular mechanisms associated with previously unrecognized pharmacological activities (9,10).

One biological process that may be relevant for exploring additional pharmacological activities of theophylline is angiogenesis. Angiogenesis is the formation of new blood vessels from pre-existing vasculature and is an important physiological process involved in tissue development, remodeling, and repair. The process is regulated by complex interactions among endothelial cells, growth factors, receptors, intracellular signaling proteins, and downstream pathways (11). Although angiogenesis is essential for normal physiological processes, dysregulated angiogenesis is also

associated with various pathological conditions. Consequently, angiogenesis represents an important biological process for investigating potential new therapeutic applications of established drugs (12,13). The potential relationship between theophylline and angiogenesis can be explored by integrating the predicted molecular targets of theophylline with genes associated with angiogenesis. In this approach, the potential molecular targets of theophylline can be obtained using a computational target-prediction platform, while angiogenesis-associated genes can be identified based on their relevance to angiogenesis. The overlapping genes between these datasets can subsequently be analyzed through protein-protein interaction networks to determine their functional relationships and network characteristics. Further functional enrichment and pathway analyses can then be used to identify biological processes and signaling pathways potentially associated with the relationship between theophylline and angiogenesis.

In the present study, network pharmacology was employed to systematically explore the potential angiogenic relevance of theophylline. The analysis was performed by identifying predicted targets of theophylline and intersecting them with angiogenesis-associated genes. The resulting overlapping targets were subsequently subjected to protein-protein interaction analysis and network-based prioritization to identify potentially important nodes within the network. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses were then performed to characterize the biological functions and signaling pathways associated with the identified targets. This integrated approach enables the potential relationship between theophylline and angiogenesis to be investigated at a systems level.

Therefore, this study aimed to explore the potential of theophylline as a drug repurposing candidate for angiogenesis-related applications using a network pharmacology approach. By integrating predicted drug targets, angiogenesis-associated genes, protein-protein interaction analysis, network prioritization, and functional pathway analysis, this study seeks to provide an initial computational framework for identifying potential biological mechanisms through which theophylline may be associated with angiogenesis and to evaluate its potential for therapeutic repurposing beyond its established respiratory use.

MATERIALS AND METHOD

Materials

The compound investigated in this study was theophylline, which was selected as a potential drug repurposing candidate. Molecular target information for theophylline was obtained from the SwissTargetPrediction (<https://www.swisstargetprediction.ch/>) database. Angiogenesis-associated genes were retrieved from the GeneCards (<https://www.genecards.org/>) database using the keyword “angiogenesis”. Only genes with a Relevance Score >50 were included in the analysis.

Additional biological and interaction data were obtained from the STRING (<https://string-db.org/>) database, while network visualization and analysis were performed using Cytoscape Version

3.10.5 software and its CytoHubba plugin. Functional enrichment analyses, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses, were performed on the overlapping target genes (<https://maayanlab.cloud/Enrichr/>).

Method

Identification of Theophylline-Associated Targets

Theophylline was used as the query compound in the SwissTargetPrediction database to identify its potential molecular targets. The canonical chemical structure of theophylline was submitted to the database, and the predicted target proteins and their corresponding gene symbols were collected for subsequent analysis.

Identification of Angiogenesis-Associated Genes

Genes associated with angiogenesis were identified using the GeneCards database. The keyword "angiogenesis" was entered into the database, and the resulting genes were collected along with their corresponding Relevance Scores. Only genes with a Relevance Score >50 were included in the subsequent analysis.

Protein-Protein Interaction Network Analysis

The predicted molecular targets of theophylline obtained from SwissTargetPrediction were compared with the angiogenesis-associated genes obtained from GeneCards. Gene symbols were standardized prior to comparison to ensure consistency between the datasets. The overlapping genes were identified as common targets potentially associated with both theophylline and angiogenesis. The identified common targets were submitted to the STRING database to construct a protein-protein interaction (PPI) network. The organism was restricted to Homo sapiens. The resulting interaction network was subsequently exported and imported into Cytoscape for network visualization and analysis.

Hub Gene Identification

The CytoHubba plugin in Cytoscape was used to identify potentially important nodes within the PPI network. The Maximal Clique Centrality (MCC) method was applied to rank the nodes according to their network centrality. Genes with higher MCC scores were considered prominent nodes within the PPI network and were evaluated for their potential biological relevance to angiogenesis.

Gene Ontology Enrichment Analysis

The common targets were subjected to Gene Ontology (GO) enrichment analysis to characterize their associated biological functions. The analysis included Biological Process (BP), Molecular Function (MF), and Cellular Component (CC) categories. The enriched GO terms were evaluated to identify biological processes, molecular functions, and cellular components potentially associated with the common targets.

KEGG Pathway Enrichment Analysis

The common targets were further analyzed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database. KEGG pathway enrichment analysis was performed to identify signaling pathways associated with the common targets. The identified pathways were subsequently evaluated based on their potential biological relevance to angiogenesis and the pharmacological actions of theophylline.

Integrated Network Pharmacology Analysis

The results from target prediction, target intersection, PPI network analysis, hub gene identification, GO enrichment, and KEGG pathway analysis were integrated to provide a systematic interpretation of the potential relationship between theophylline and angiogenesis. The resulting molecular networks and enriched pathways were used to generate hypotheses regarding the potential biological mechanisms underlying the angiogenesis-related activity of theophylline.

RESULT AND DISCUSSION

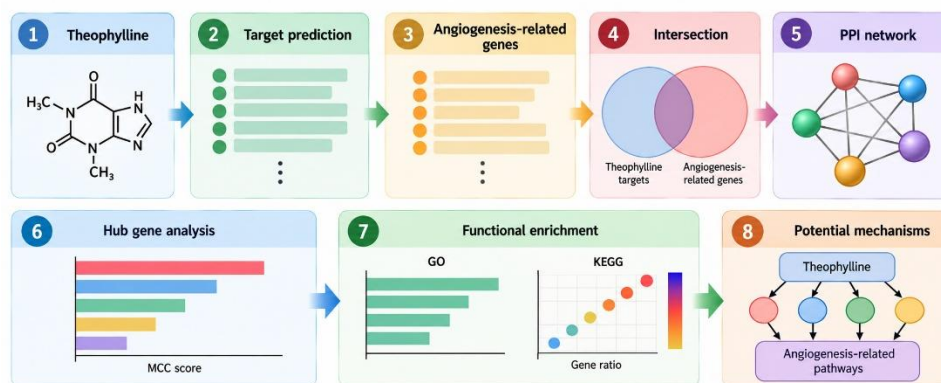


Figure 1. Schematic workflow of the network pharmacology analysis of theophylline for exploring its potential association with angiogenesis.

SwissTargetPrediction analysis identified multiple potential molecular targets of theophylline, reflecting its broad pharmacological profile. The highest predicted probabilities were observed for the adenosine receptor family, including ADORA1, ADORA2A, ADORA2B, and ADORA3, each with a prediction probability of 1.000. Several phosphodiesterase (PDE) family members were also predicted, including PDE3A, PDE3B, PDE5A, and PDE2A, with a prediction probability of 0.804. The identification of adenosine receptors and phosphodiesterases among the predicted targets is consistent with the known pharmacological characteristics of theophylline and supports its multi-target pharmacological profile. From a drug repurposing perspective, the presence of multiple predicted targets provides a rational basis for investigating biological activities beyond the conventional respiratory applications of theophylline. However, these target predictions represent computational estimations and do not independently establish direct target binding or biological activity.

To investigate the potential association between theophylline and angiogenesis, the predicted targets of theophylline were compared with angiogenesis-associated genes obtained from

GeneCards using a Relevance Score threshold greater than 50. The intersection analysis identified six common genes: KDR, EPHB4, SRC, TYMP, JAK2, and PDE3B. The presence of these overlapping genes indicates that several predicted molecular targets of theophylline are also associated with angiogenesis-related biological processes. The identified targets represent different functional classes, including receptor tyrosine kinases, intracellular tyrosine kinases, and phosphodiesterases. This diversity is relevant to angiogenesis because vascular formation is regulated by interconnected molecular pathways rather than by a single molecular target. Nevertheless, the identification of overlapping genes should be interpreted as a computational association and does not demonstrate that theophylline directly regulates angiogenesis.

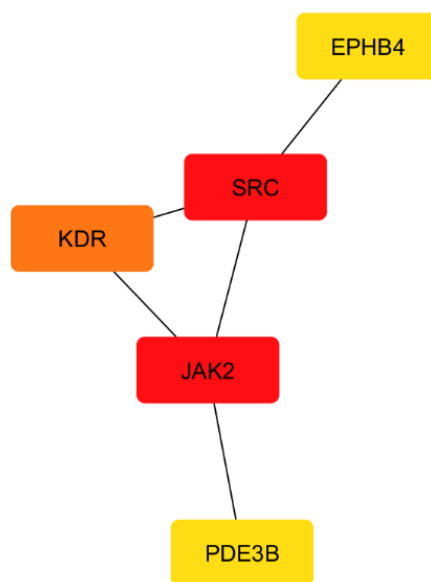


Figure 2. Protein-protein interaction network of the common targets associated with theophylline and angiogenesis.

The six common targets were subsequently evaluated using protein-protein interaction analysis. The resulting network demonstrated interactions among EPHB4, SRC, KDR, JAK2, and PDE3B, whereas TYMP was not incorporated into the connected PPI network observed in the analysis. The interaction pattern indicates that several of the identified targets are functionally interconnected. EPHB4 and KDR are receptor-associated proteins, whereas SRC and JAK2 function as intracellular signaling proteins. The presence of these proteins within the same interaction network suggests that the potential relationship between theophylline and angiogenesis may involve interconnected signaling mechanisms rather than independent target effects. PDE3B was also present within the connected network, despite belonging to a different class of molecular target. Its presence is particularly notable because it showed a relatively high prediction probability in SwissTargetPrediction. This finding illustrates that target prediction probability and network centrality represent different aspects of molecular relevance. A protein may have a relatively high probability of interacting with theophylline without necessarily occupying a highly connected position within the angiogenesis-associated network.

CytoHubba analysis using the Maximal Clique Centrality method further demonstrated differences in the network importance of the identified proteins. SRC and JAK2 were ranked as the highest nodes in the network, followed by KDR, PDE3B, and EPHB4. The high MCC values of SRC and JAK2 indicate that these proteins occupy prominent positions within the identified interaction network. SRC is an intracellular tyrosine kinase involved in signal transduction from multiple receptor systems, while JAK2 is an important mediator of intracellular signaling associated with several receptor pathways. Their high network centrality suggests that these proteins may function as important signaling connections within the molecular network associated with the overlapping targets. Although KDR showed a lower MCC ranking than SRC and JAK2, its biological relevance remains notable because of its established association with vascular signaling. Similarly, PDE3B and EPHB4 remained part of the connected network despite their lower centrality scores. Therefore, network ranking should not be considered independently but should be interpreted together with target prediction and functional enrichment results.



Figure 3. Gene Ontology enrichment analysis of the common targets based on Molecular Function (MF).

Gene Ontology enrichment analysis provided additional information regarding the biological functions associated with the common targets. The Molecular Function analysis identified protein tyrosine kinase activity, SH2 domain binding, non-membrane spanning protein tyrosine kinase activity, transmembrane receptor protein kinase activity, and transmembrane receptor protein tyrosine kinase activity among the enriched functions. Vascular endothelial growth factor receptor activity was also identified. These findings are consistent with the composition of the common-target network, which contains several receptor and non-receptor tyrosine kinases. The identification of vascular endothelial growth factor receptor activity is particularly relevant to the focus of the present study because VEGF-mediated signaling represents an important regulatory mechanism in angiogenesis.

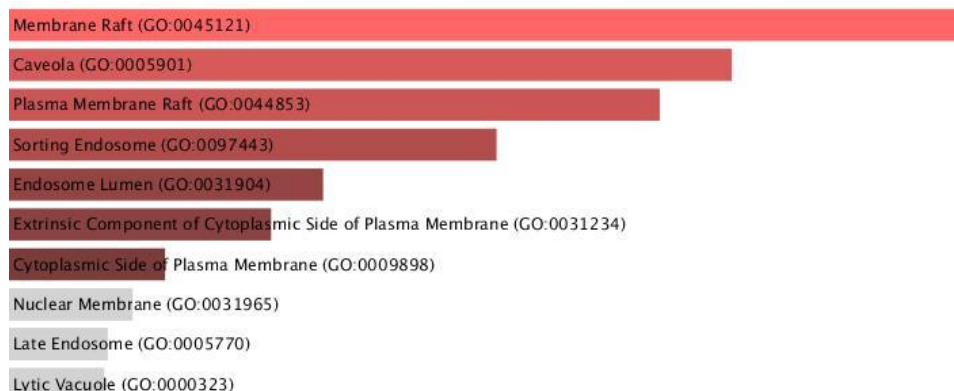


Figure 4. Gene Ontology enrichment analysis of the common targets based on Cellular Component (CC)

The Cellular Component analysis identified several membrane-associated compartments, including membrane rafts, caveolae, plasma membrane rafts, sorting endosomes, endosome lumen, and the cytoplasmic side of the plasma membrane. These cellular locations are compatible with the involvement of membrane-associated receptors and intracellular signaling proteins in the identified network. The Biological Process analysis further identified cell surface receptor protein tyrosine kinase signaling, regulation of PI3K/AKT signaling, peptidyl-tyrosine phosphorylation, interleukin-6-mediated signaling, cellular response to interleukin-6, VEGF receptor signaling, and protein phosphorylation. The identification of VEGF receptor signaling and PI3K/AKT-related processes provides an additional biological context connecting the identified molecular targets with angiogenesis-related signaling.

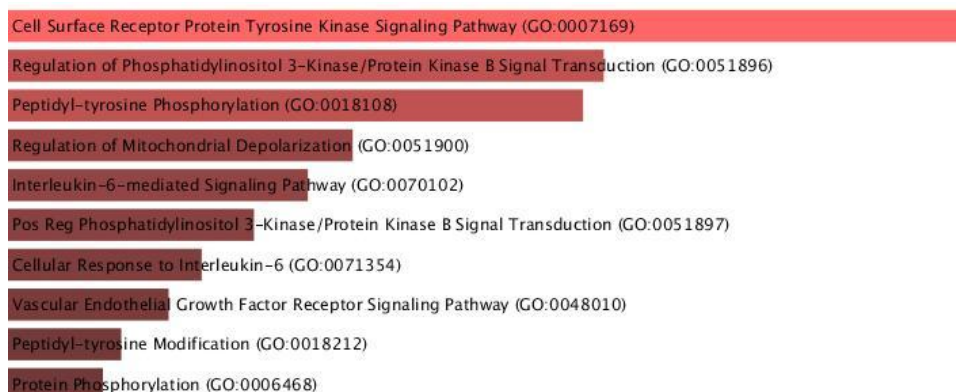


Figure 5. Gene Ontology enrichment analysis of the common targets based on Biological Process (BP).

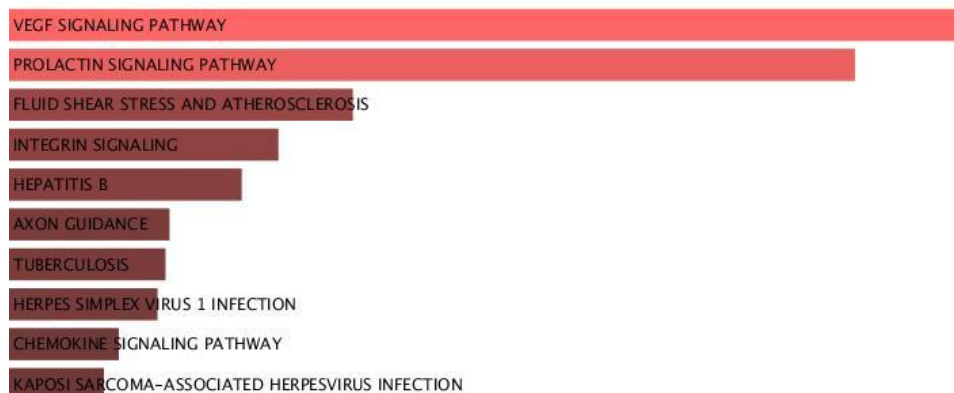


Figure 6. KEGG pathway enrichment analysis of the common targets.

KEGG pathway analysis identified several pathways associated with the common targets, including the VEGF signaling pathway, prolactin signaling pathway, fluid shear stress and atherosclerosis, integrin signaling, axon guidance, chemokine signaling, and several infection-associated pathways. Among these pathways, the VEGF signaling pathway is particularly relevant to the objective of the present study. The VEGF signaling pathway plays an important role in the regulation of endothelial responses and vascular development. Its identification in the enrichment analysis therefore provides additional computational support for the potential association between theophylline-associated targets and angiogenesis-related mechanisms. The identification of integrin signaling and fluid shear stress and atherosclerosis pathways also suggests that the common targets may participate in broader vascular and cellular signaling processes.

Several infection-associated pathways were also identified in the KEGG analysis. However, their presence should not be interpreted as evidence that theophylline possesses therapeutic activity against the corresponding infectious diseases. Pathway enrichment can occur because multiple pathways share signaling proteins or molecular components with the analyzed target set. Therefore, these pathways should be interpreted in the context of the molecular functions of the identified targets rather than solely based on their pathway names.

Overall, the integrated network pharmacology analysis provides a computational framework linking theophylline with angiogenesis-associated molecular mechanisms. The initial target prediction demonstrated that theophylline has a broad predicted target profile involving several receptor and enzyme families. The subsequent intersection with angiogenesis-associated genes identified six common targets, of which five formed a connected PPI network. Network analysis further identified SRC and JAK2 as the most prominent nodes based on MCC, while KDR, PDE3B, and EPHB4 were also retained within the connected network. The enrichment analyses subsequently demonstrated associations with tyrosine kinase activity, VEGF receptor activity, PI3K/AKT regulation, and VEGF receptor signaling, while KEGG analysis identified the VEGF signaling pathway. The convergence of these findings suggests that the potential relationship between theophylline and angiogenesis may involve multiple interconnected signaling mechanisms rather than a single molecular target.

From a drug repurposing perspective, these findings provide an initial computational rationale for further investigating theophylline beyond its established respiratory applications. However, the results should be interpreted cautiously because all analyses performed in this study are computational. SwissTargetPrediction provides predicted drug-target associations, GeneCards Relevance Scores represent database-derived associations with angiogenesis, PPI analysis describes reported or predicted protein interactions, and GO and KEGG analyses identify associations between the analyzed targets and biological functions or pathways. None of these approaches independently demonstrates that theophylline produces an angiogenic effect or confirms its therapeutic efficacy.

CONCLUSION

This study explored the potential of theophylline as a drug repurposing candidate for angiogenesis-related applications using an integrated network pharmacology approach. The analysis identified six common targets between the predicted molecular targets of theophylline and angiogenesis-associated genes, namely KDR, EPHB4, SRC, TYMP, JAK2, and PDE3B. Protein-protein interaction analysis demonstrated that EPHB4, SRC, KDR, JAK2, and PDE3B formed a connected interaction network, with SRC and JAK2 identified as the most prominent nodes based on MCC analysis.

Gene Ontology enrichment analysis indicated that the common targets were associated with protein tyrosine kinase activity, transmembrane receptor protein kinase activity, vascular endothelial growth factor receptor activity, and regulation of PI3K/AKT signaling. Furthermore, KEGG pathway analysis identified the VEGF signaling pathway among the enriched pathways. These findings suggest that theophylline may have a potential molecular association with angiogenesis-related signaling through multiple interconnected targets and biological pathways.

However, the findings of this study are based entirely on computational analyses and should therefore be considered hypothesis-generating rather than evidence of therapeutic efficacy. The identified molecular associations do not establish that theophylline directly promotes or regulates angiogenesis. Further experimental validation through appropriate *in vitro* and *in vivo* studies is required to confirm the predicted biological mechanisms and determine whether theophylline has potential for therapeutic application in angiogenesis-related conditions.

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