Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI:10.67145/yzw31p02

NETWORK PHARMACOLOGY-BASED INVESTIGATION OF CATECHIN, EPIGALLOCATECHIN, AND EPIGALLOCATECHIN GALLATE AGAINST BREAST AND LUNG CANCER

Nayakanti Bhasker Babu[1], Donakonda Madhuri[2]
[1*]Research Scholar, JNTUA. Ananthapur, Andhra Pradesh, Creative Educational Society's College of Pharmacy, JNTUA, Kurnool, AndhraPradesh, 518218, madhurisatyasai@gmail.com
[2]Creative Educational Society's College of Pharmacy, JNTUA, Kurnool, Andhra Pradesh, 518218, bhasker.nayakanti@gmail.com
Institution Email: cescop2006@gmail.com

Abstract
Background of the study:
Breast and lung cancers are complex diseases influenced by multiple factors, involving intricate molecular changes and disrupted signalling pathways. Catechin, epigallocatechin (EGC), and epigallocatechin gallate (EGCG) are flavan-3-ols found in nature that have shown potential in cancer treatment. This study focused on identifying shared molecular targets of these catechins in breast and lung cancers using a network pharmacology method. Information on targets related to catechin, EGC, and EGCG was sourced from the SWISS target prediction, PubChem database, while genes linked to breast and lung cancers were gathered from GeneCards. Common targets were pinpointed using Venny 2.1, and protein–protein interactions were analyzed using the STRING database.. A total of 101 targets related to compounds were discovered, alongside 21,768 genes linked to breast cancer and 24,525 genes associated with lung cancer. Through Venny analysis, three shared targets were identified: sclerostin (SOST), transthyretin (TTR), and tyrosinase (TYR). STRING analysis revealed that these three proteins do not directly interact under the specified interaction conditions. The functional interpretation highlighted connections with Wnt/bone-related signaling, processes associated with transthyretin, tyrosine metabolism, and melanogenesis. In summary, the results imply that catechin, EGC, and EGCG might engage with various molecular targets linked to breast and lung cancer. These findings offer initial mechanistic insights into the potential anticancer effects of the selected catechins and suggest the need for further experimental validation.

Keywords: Catechin, epigallocatechin, epigallocatechin gallate, lung cancer, and breast cancer.

Introduction

Cancer is a complex disease with multiple contributing factors, including unchecked cell growth, evasion of programmed cell death, persistent formation of new blood vessels, invasion, metastasis, and significant molecular changes. Even with significant progress in surgical methods, chemotherapy, radiotherapy, targeted treatments, and immunotherapy, cancer remains a significant global health challenge. The International Agency for Research on Cancer (IARC) reported that in 2022, there were approximately 20 million new cancer cases and 9.7 million deaths related to cancer worldwide. Lung cancer emerged as the most diagnosed cancer and the primary cause of cancer-related deaths, while female breast cancer was the second most diagnosed cancer globally [1]. The

substantial incidence and mortality associated with these malignancies emphasize the need for the identification of safer and mechanistically diverse therapeutic or chemopreventive strategies.

Breast cancer is characterized by its heterogeneity, encompassing various molecular subtypes and intricate genetic and signaling irregularities. The disruption of pathways related to cell growth, programmed cell death, oxidative stress, inflammation, new blood vessel formation, epithelial–mesenchymal transition, and hormone-driven signaling plays a role in the onset and advancement of breast cancer. Despite progress in molecular classification and targeted treatments enhancing clinical results, challenges such as therapeutic resistance, recurrence, metastasis, and side effects from treatments persist as significant issues [2]. Similarly, lung cancer consists of biologically diverse malignancies, mainly non-small-cell lung cancer and small-cell lung cancer, where irregularities in receptor tyrosine kinase signaling, PI3K/AKT, MAPK, NF-κB, cell-cycle control, apoptosis, and epithelial–mesenchymal transition contribute to disease advancement [3]. Consequently, therapeutic strategies that can concurrently target multiple molecular pathways may hold particular promise for treating complex cancers.

Natural products have attracted considerable attention in cancer research because of their structural diversity and ability to modulate several biological processes simultaneously. Among the naturally occurring polyphenolic compounds, tea catechins have been extensively investigated for their antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, antiangiogenic, and antimetastatic properties [4,5]. Catechins and their structurally related derivatives are important members of the flavan-3-ol family. Catechins (C), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG) possess closely related chemical structures but differ in their hydroxylation and galloylation patterns, which may influence their biological interactions and molecular targets. EGCG, in particular, is one of the most extensively studied catechins and is considered a major bioactive polyphenol present in green tea [4,5].

Increasing experimental evidence suggests that catechins may interfere with several molecular events involved in the carcinogenesis. In breast cancer models, green tea catechins have been reported to inhibit cancer cell proliferation, induce apoptosis, influence cell cycle progression, modulate redox signaling, and affect molecular processes associated with invasion and metastasis [6]. EGCG has garnered particular attention because it regulates multiple signaling pathways involved in tumor growth and survival. Reported mechanisms include the modulation of PI3K/AKT, MAPK, JAK/STAT, Wnt, NF-κB, and other oncogenic pathways, as well as effects on apoptosis, angiogenesis, cell cycle regulation, and epigenetic processes [5,7]. A systematic review of EGCG in breast cancer reported evidence of inhibition of cell proliferation and cell cycle progression, induction of apoptosis, suppression of metastasis, and inhibition of angiogenic processes in experimental models [8].

The potential relevance of tea catechins to breast cancer is also supported by epidemiological investigations, although the findings are not completely consistent. A systematic review and meta-analysis reported that higher green tea consumption was associated with a modest reduction in breast cancer risk in case-control studies, while the evidence from cohort studies was less conclusive [9]. Earlier meta-analyses similarly suggested possible inverse associations between green tea consumption and breast cancer recurrence or incidence, but emphasized the limitations in the available epidemiological evidence [10]. These observations support further investigation of the molecular mechanisms underlying the anticancer effects of individual catechins rather than relying solely on epidemiological associations.

Lung cancer is another important target for investigating the anti-cancer potential of tea-derived polyphenols. Experimental studies have demonstrated that EGCG inhibits lung cancer cell proliferation, induces apoptosis and cell cycle arrest, suppresses migration and invasion, and interferes with several oncogenic signaling pathways [11]. Recent evidence indicates that EGCG can modulate EGFR-associated signaling and downstream PI3K/AKT, MAPK/ERK, and mTOR pathways, in addition to influencing oxidative stress, apoptosis, ferroptosis, epithelial–mesenchymal transition, and cancer stem cell-associated mechanisms [11,12]. Epidemiological studies have also suggested a possible inverse association between green tea consumption and lung cancer risk;

however, these findings should be interpreted cautiously because observational evidence cannot establish the direct therapeutic effect of individual catechins [13,14].

Although considerable experimental evidence exists regarding the anticancer properties of EGCG, the biological actions of catechin, EGC, and EGCG are potentially multidimensional and may involve overlapping molecular targets across different cancer types. Conventional single-target approaches may therefore provide an incomplete understanding of their pharmacological actions. Systems-level approaches, such as network pharmacology, offer an opportunity to investigate interactions between bioactive compounds, disease-associated genes, proteins, signaling pathways, and biological processes. Network pharmacology integrates pharmacological and systems-biology concepts to investigate the multicomponent–multitarget nature of bioactive molecules and can facilitate the identification of potential therapeutic targets and mechanisms [15].

In the present study, target information associated with catechin, epigallocatechin, and epigallocatechin gallate was integrated with gene sets related to breast and lung cancers. Venny 2.0 was used to identify overlapping genes between the compound-associated and cancer-associated datasets, enabling the identification of candidate genes potentially linking the selected catechins with both malignancies [16]. The common targets were subjected to protein–protein interaction (PPI) network analysis using the STRING database, which integrates experimental and computational evidence to identify functional and physical associations among proteins [17]. STRING confidence scores provide an estimate of the reliability of protein associations and facilitate the identification of interconnected molecular networks [17,18].

Further network pharmacology analysis can provide insight into the biological significance of the identified common targets through functional enrichment, pathway analysis, and network topology. Such an approach is particularly relevant for catechins because their reported anticancer effects involve multiple signaling pathways rather than a single molecular target. By integrating compound-associated targets, cancer-related genes, common targets, protein-protein interaction relationships, and pathway-level information, the present study aims to provide a systems-level understanding of the potential molecular mechanisms through which catechin, epigallocatechin, and epigallocatechin gallate may influence breast cancer and lung cancer.

Therefore, the present study was designed to explore the potential anticancer mechanisms of catechin, epigallocatechin, and EGCG using an integrated network pharmacology approach, with an emphasis on the identification of common therapeutic targets, PPI interactions, and biologically relevant signaling pathways associated with breast and lung cancers. These findings may provide mechanistic hypotheses for further experimental validation and contribute to the identification of potential molecular targets of these naturally occurring catechins.

Methodology

2.1Retrieval of compound-related information

The selected compounds, catechin, epigallocatechin (EGC), and epigallocatechin gallate (EGCG), were investigated using the SWISS target prediction, PubChem database. Chemical and biological information, including compound identifiers and available target-associated information, were retrieved for each compound [19]. Only human-associated targets were considered, and duplicate entries were removed before further analyses.

2.2. Collection of cancer-associated genes

Disease-associated genes for breast and lung cancers were retrieved from the GeneCards database using the respective disease names as search terms. The obtained gene lists were compiled, standardized to human gene symbols, and duplicate entries were removed [20,21].

2.3. Identification of common targets

Compound-related targets were compared with breast cancer- and lung cancer-associated genes using Venny 2.1. Separate Venn analyses were performed for catechin, EGC, and EGCG against each cancer dataset. Overlapping genes were considered common targets potentially associated with the anticancer activity of the selected compounds [22].

2.4. Protein–protein interaction analysis

The identified common targets were submitted to the STRING database for protein–protein interaction (PPI) analysis. The species were restricted to Homo sapiens. The interaction network was generated based on known and predicted functional associations among the proteins [23,24]. Highly interconnected nodes were considered potential hub targets and were further evaluated for their relevance to cancer-related mechanisms.

2.5. Network pharmacology and pathway analysis

An integrated compound–target–disease network was constructed to investigate the potential multitarget mechanisms of catechin, EGC, and EGCG against breast and lung cancers. The common targets and hub genes were further examined using functional enrichment and pathway analyses, including Gene Ontology (GO) and KEGG pathway analyses, available through STRING [23,24]. The enriched pathways were interpreted in relation to cancer-associated processes, such as cell proliferation, apoptosis, cell-cycle regulation, inflammation, and tumor progression.

Results and discussion

3.1. Identification of common targets

Target analysis identified 101 targets for each of the selected compounds: catechin, epigallocatechin (EGC), and epigallocatechin gallate (EGCG). GeneCards analysis yielded 21,768 genes associated with breast cancer and 24,525 genes associated with lung cancer. Venny 2.1 analysis revealed three common genes—SOST, TTR, and TYR—shared between the compound-related targets and both breast- and lung-cancer-associated gene sets (Figure 1–3).

Interestingly, the same three targets were identified for catechin, EGC, and EGCG, suggesting that these structurally related catechins may have overlapping molecular associations with the selected cancer datasets. The identification of common targets supports the possibility of a multitarget mechanism; however, these computational overlaps should be regarded as candidate targets rather than confirmed therapeutic targets for further validation.

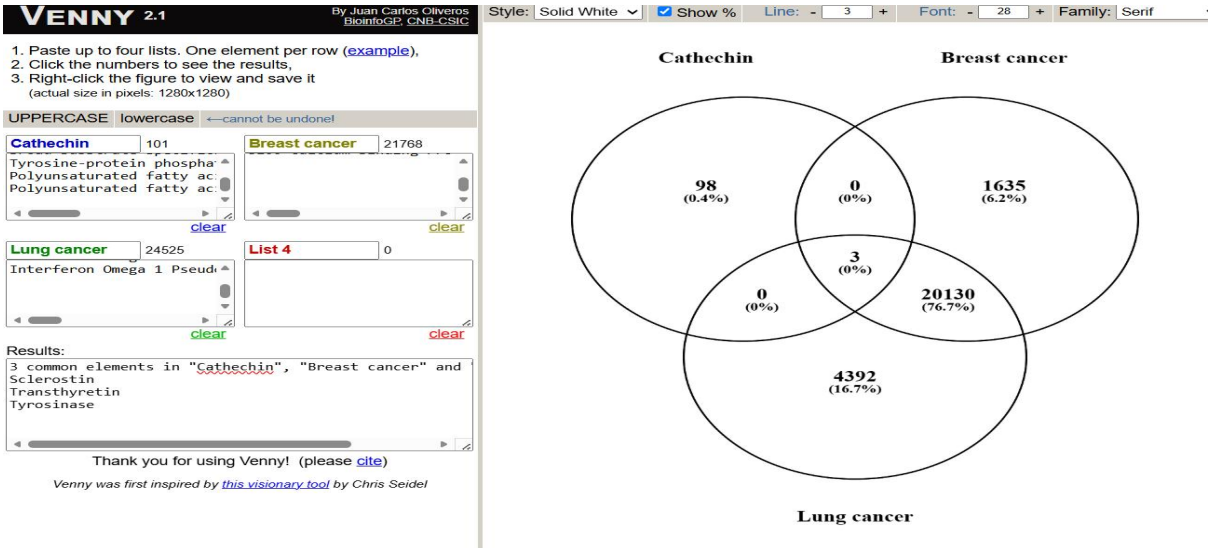

Figure 1. Venn diagram showing the common targets of catechin-associated genes and breast cancer-associated genes

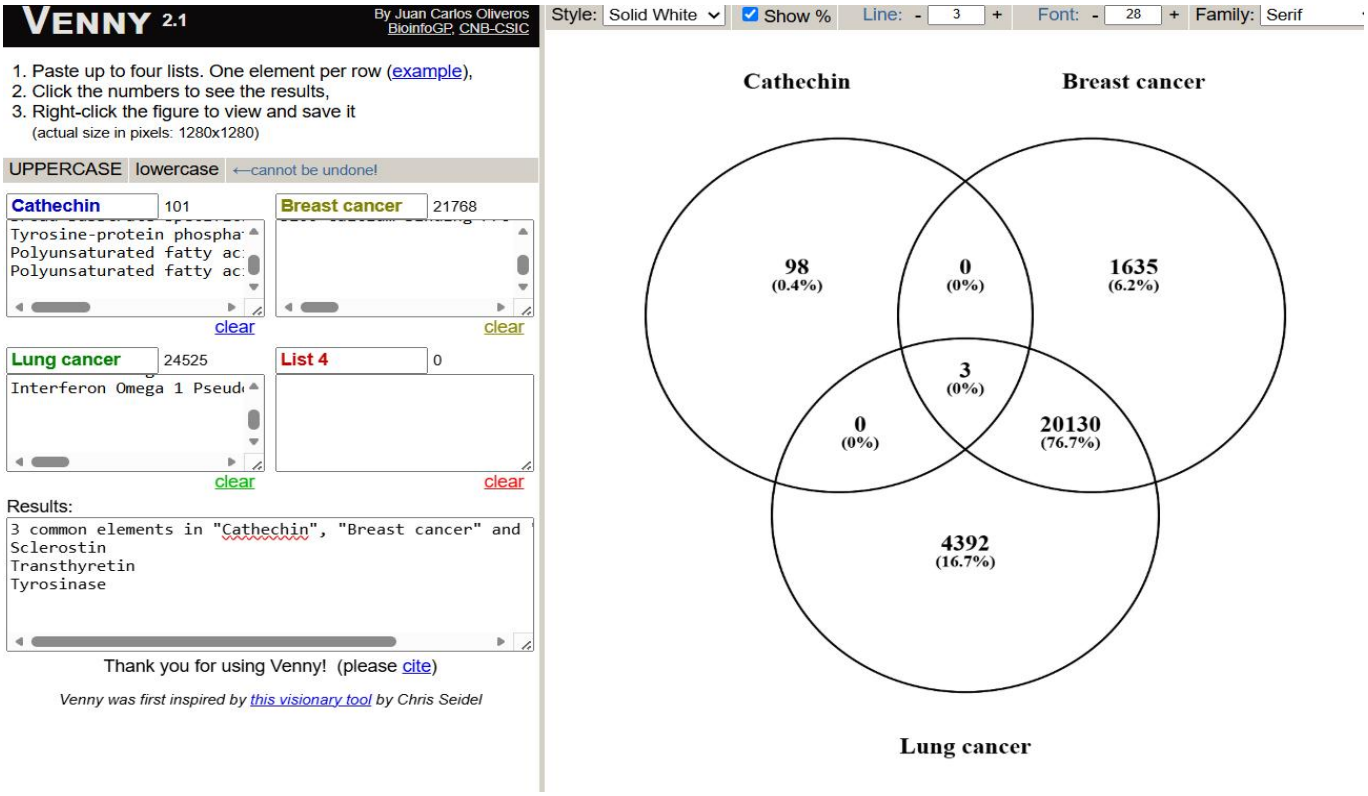

Figure 2. Venn diagram showing the common targets of epigallocatechin-associated genes and breast cancer-associated genes

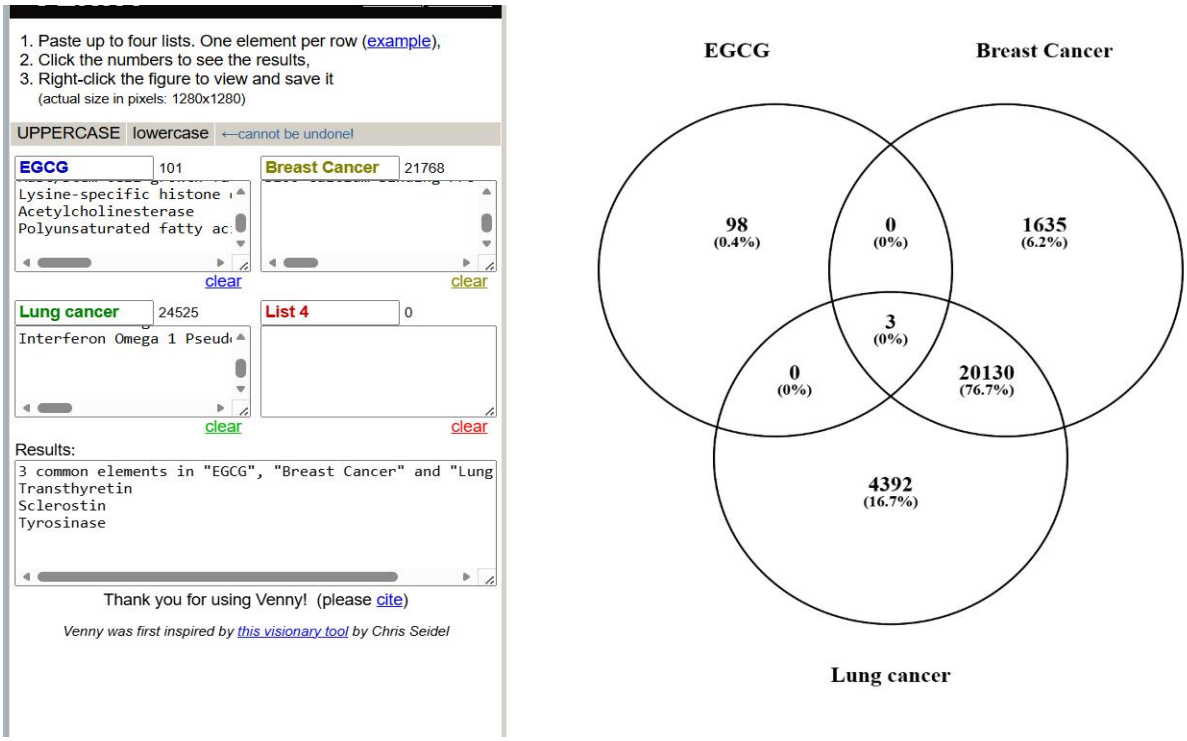

Figure 3. Venn diagram showing the common targets of epigallocatechin gallate-associated genes and breast cancer-associated genes

3.2. Protein–protein interaction analysis

The three common targets, SOST, TTR, and TYR, were subsequently analyzed using the STRING database to explore their functional associations. The resulting PPI network contained three nodes corresponding to sclerostin, transthyretin, and tyrosinase. As shown in the uploaded STRING output, no connecting edges were observed among the three proteins under the selected network conditions. (Figure 4)

The absence of direct PPI connections indicates that these proteins may represent functionally distinct molecular targets rather than closely interconnected protein complexes. This finding is important because STRING associations represent functional relationships and not necessarily direct physical binding; therefore, the absence of an edge does not exclude biological relevance of the interaction. STRING integrates evidence from experiments, curated databases, co-expression, text mining, and computational predictions to generate protein association networks [25,26].

Figure 4. Protein–protein interaction network of the common targets identified between catechin, epigallocatechin, epigallocatechin gallate, breast cancer, and lung cancer

3.3. Biological relevance of SOST

Among the identified common targets, SOST encodes sclerostin, an extracellular protein known to negatively regulate canonical Wnt signaling. The identification of SOST is of particular interest because Wnt signaling is involved in cellular proliferation, differentiation, and tumor progression. Experimental studies have demonstrated a relationship between sclerostin and breast cancer-associated bone metastasis, indicating that alteration of SOST/Wnt signaling may influence the tumor–bone microenvironment. [25]

Therefore, the present network analysis suggests that SOST may represent a potential molecular link between the selected catechins and cancer-associated signaling. However, because the current analysis is based on target overlap, it cannot establish whether catechin, EGC, or EGCG activates or inhibits SOST. Further experimental validation is required to establish the direction and biological significance of this interaction.

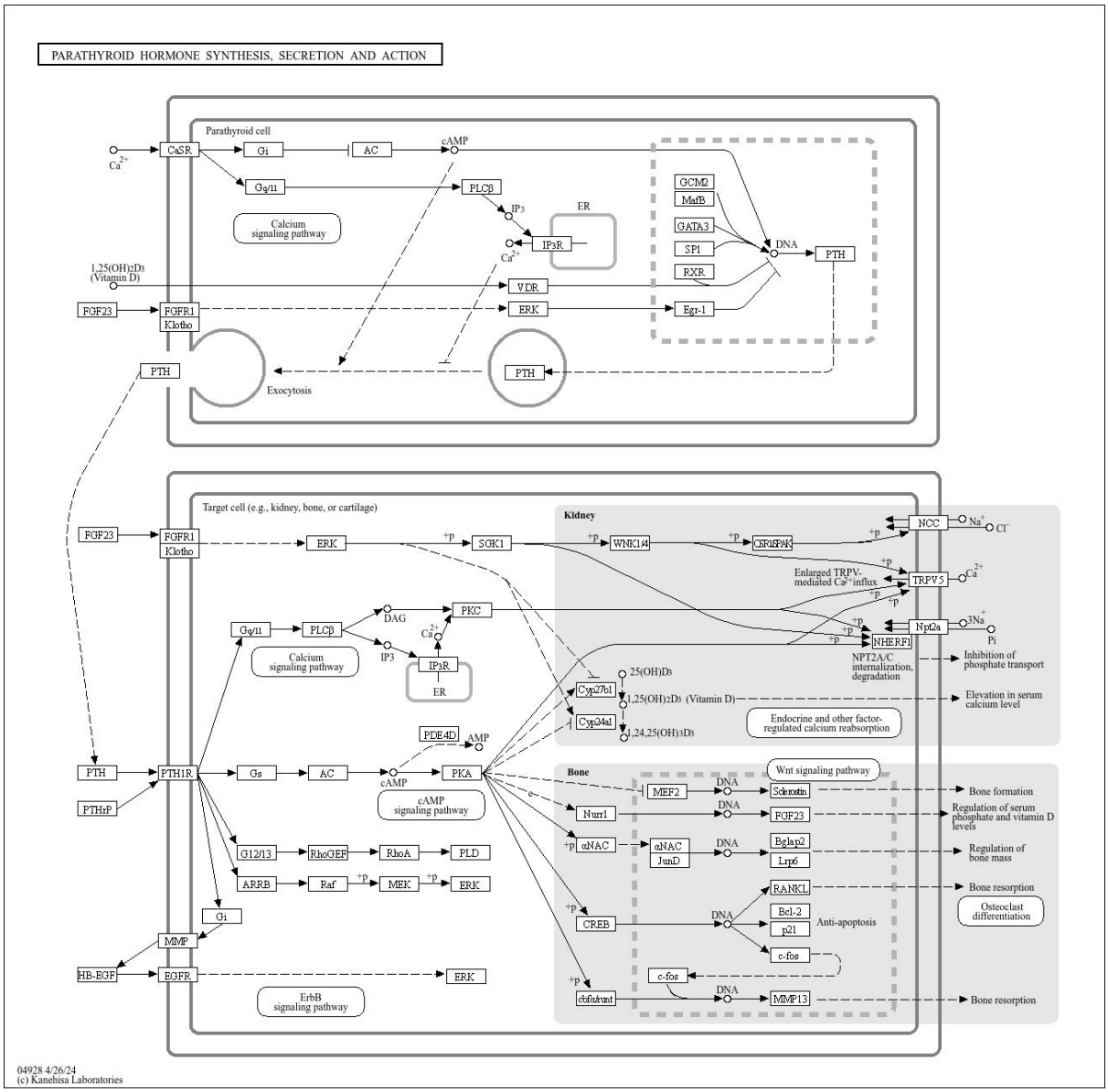

Figure 5: KEGG pathway enrichment analysis of sclerostin

3.4. Biological relevance of TTR

TTR encodes transthyretin, a protein involved primarily in thyroid hormone and retinol transport. Its identification as a common target is noteworthy because altered TTR expression has been reported in both breast and lung cancer-related investigations. A serum proteomic study identified transthyretin among a panel of proteins capable of differentiating breast cancer patients from healthy individuals.

Similarly, TTR expression has been investigated in lung cancer, with studies reporting altered TTR expression in lung cancer tissue and serum. Experimental evidence has also linked TTR to proliferation and signaling pathways in non-small-cell lung cancer. Thus, the identification of TTR in the present analysis provides a potentially relevant molecular connection between the selected catechins and lung- and breast cancer-associated biological processes. Nevertheless, the precise role of TTR may be context-dependent and requires further experimental confirmation.

3.5. Biological relevance of TYR

TYR encodes tyrosinase, which is a key enzyme involved in tyrosine metabolism and melanogenesis. The present study identified TYR as a common target of all three catechins. KEGG mapping confirmed that TYR participates in the melanogenesis pathway (hsa04916) and tyrosine metabolism.

The association of TYR with cancer has historically been investigated, particularly in malignant melanoma; however, altered tyrosinase activity has also been reported in studies involving breast and lung malignancies. Earlier investigations reported increased serum tyrosinase activity in breast and lung carcinomas; however, the biological significance and specificity of these observations remain uncertain. Therefore, the identification of TYR in the present network should be interpreted as a computationally identified cancer-associated target, rather than evidence that tyrosinase is a principal driver of breast or lung cancer.

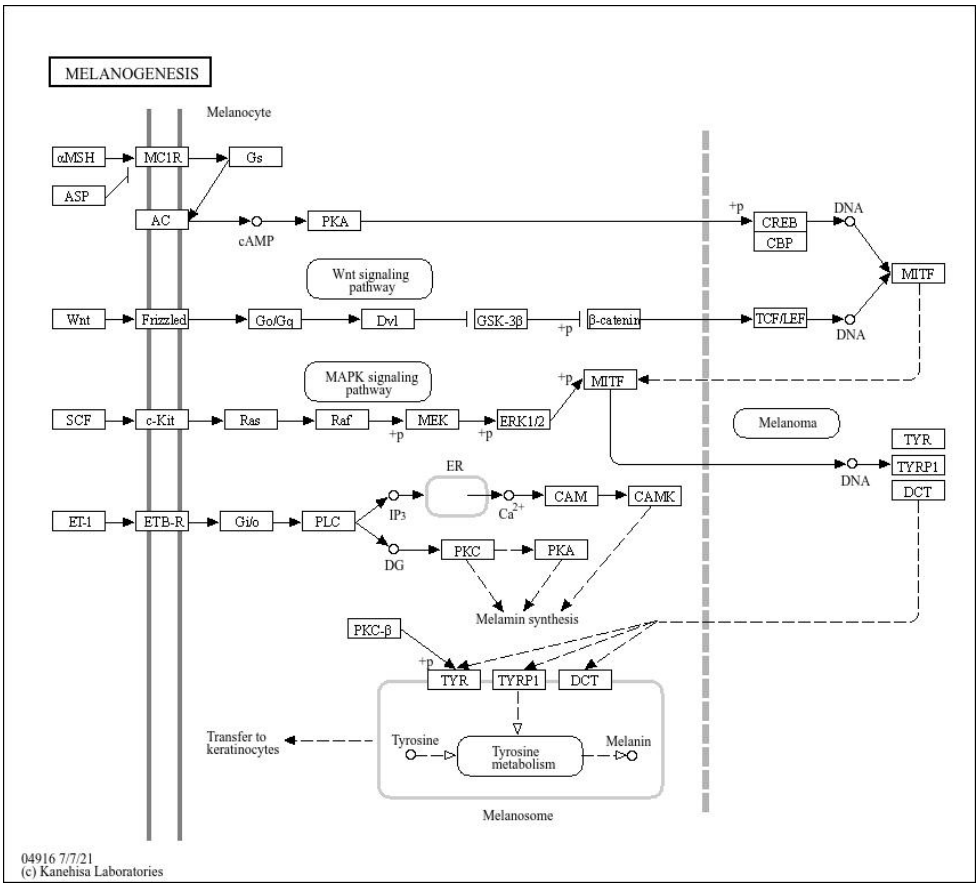

Figure 6: KEGG pathway enrichment analysis of tyrosinase

3.6. Pathway analysis of the identified targets

Pathway mapping of the identified common targets indicated involvement of melanogenesis and parathyroid hormone synthesis, secretion, and action. TYR is directly represented in the human melanogenesis pathway, where it functions as a key enzyme involved in melanin biosynthesis.

The SOST gene is included in the human parathyroid hormone synthesis, secretion, and action pathway, particularly in relation to Wnt-associated regulation of bone formation. This finding may be relevant to the established interaction between cancer and the bone microenvironment, particularly in cancers such as breast cancer, in which skeletal metastasis is clinically important.

Importantly, these pathway associations should not be interpreted as evidence that the selected catechins directly regulate melanogenesis or parathyroid hormone signaling in breast or lung cancer. Rather, they indicate that the identified common targets are annotated within these biological pathways. Further pathway-specific experimental studies are required to determine the relevance of catechin, EGC, and EGCG to anticancer activity. [26-28]

Conclusion

Collectively, network pharmacology analysis identified SOST, TTR, and TYR as three common molecular targets shared by catechin, EGC, and EGCG in the breast and lung cancer datasets. The

presence of the same targets for all three catechins suggests a degree of molecular overlap between these structurally related compounds. However, STRING analysis did not demonstrate direct interactions among SOST, TTR, and TYR, indicating that their potential biological contributions may occur through independent or indirectly connected mechanisms.

Overall, these findings provide a preliminary systems-level hypothesis that catechin, EGC, and EGCG may be associated with cancer-relevant molecular processes involving Wnt/bone-related signaling, transthyretin-associated processes, and tyrosine/melanogenesis-related pathways. These results should be considered exploratory and require validation using molecular, cellular and in vivo approaches.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–263. doi:10.3322/caac.21834.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249.
3. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018;553:446–454.
4. Cabrera C, Artacho R, Giménez R. Beneficial effects of green tea—a review. J Am Coll Nutr. 2006;25(2):79–99.
5. Khan N, Afaq F, Saleem M, Ahmad N, Mukhtar H. Targeting multiple signaling pathways by green tea polyphenol (-)-epigallocatechin-3-gallate. Cancer Res. 2006;66(5):2500–2505.
6. Thangapazham RL, Passi N, Maheshwari RK. Green tea polyphenol and its chemopreventive and therapeutic effects on breast cancer. Cancer Lett. 2007;245(1–2):74–85.
7. Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem Pharmacol. 2011;82(12):1807–1821.
8. Farabegoli F, Papi A, Orlandi M. (-)-Epigallocatechin-3-gallate: a review of its chemopreventive effects in breast cancer. Molecules. 2011;16(6):4731–4747.
9. Filippini T, Malavolti M, Borrelli F, et al. Green tea consumption and breast cancer risk: a systematic review and meta-analysis of observational studies. Nutrients. 2020.The broader evidence base indicates that epidemiological findings are mixed; a previous systematic review/meta-analysis found a modest reduction in breast cancer risk among women with higher green-tea consumption in case-control studies.
10. Seely D, Mills EJ, Wu P, Verma S, Guyatt GH. The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: a systematic review and meta-analysis. Integr Cancer Ther. 2005;4(2):144–155.
11. Aggarwal V, Tuli HS, Tania M, et al. Molecular mechanisms of action of epigallocatechin gallate in cancer: recent trends and advancement. Semin Cancer Biol. 2022;80:256–275. doi:10.1016/j.semcancer.2020.05.011.
12. Mirbabaei Ghafghazi D, Sze NSK, Tsiani E. Effects of epigallocatechin gallate against lung cancer: mechanisms of action and therapeutic potential. Nutrients. 2026;18(3):378. doi:10.3390/nu18030378.
13. Tang N, Wu Y, Zhou B, Wang B, Yu R. Green tea, black tea consumption and risk of lung cancer: a meta-analysis. Lung Cancer. 2009;65(3):274–283. doi:10.1016/j.lungcan.2008.12.002.
14. Wang H, Zhou Y, Yu D, Zhu H, Wang J, et al. Tea consumption and lung cancer risk: a meta-analysis of case-control and cohort studies. Nutr Cancer. 2014.

15. Liu X, Wu WY, Jiang BH, Yang M, Guo DA. Pharmacological tools for the development of traditional Chinese medicine. Trends Pharmacol Sci. 2013;34(11):620–628. doi:10.1016/j.tips.2013.09.004.
16. Hulsen T, de Vlieg J, Alkema W. BioVenn – a web application for the comparison and visualization of biological lists using area-proportional Venn diagrams. BMC Genomics. 2008;9:488. Venn-diagram approaches are widely used to visualize intersections between biological datasets.
17. Szklarczyk D, Gable AL, Lyon D, et al. STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 2019;47(D1):D607–D613.
18. Szklarczyk D, Kirsch R, Koutrouli M, et al. The STRING database in 2023: protein–protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res. 2023;51(D1):D638–D646
19. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem 2023 update. Nucleic Acids Res. 2023;51(D1):D1373–D1380. doi:10.1093/nar/gkac956.
20. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards Suite: from gene data mining to disease genome sequence analyses. Curr Protoc Bioinformatics. 2016;54:1.30.1–1.30.33. doi:10.1002/cpbi.5.
21. Safran M, Dalah I, Alexander J, Rosen N, Stein TI, Shmoish M, et al. GeneCards Version 3: the human gene integrator. Database (Oxford). 2010;2010:baq020. doi:10.1093/database/baq020.
22. Oliveros JC. Venny. An interactive tool for comparing lists with Venn's diagrams. Venny 2.1.0. BioinfoGP, CNB-CSIC.
23. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 2019;47(D1):D607–D613. doi:10.1093/nar/gky1131.
24. Szklarczyk D, Kirsch R, Koutrouli M, Nastou KC, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein–protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res. 2023;51(D1):D638–D646. doi:10.1093/nar/gkac1000.
25. Hiraga T, Horibe K, Koide M, Yamashita T, Kobayashi Y. Sclerostin blockade promotes bone metastases of Wnt-responsive breast cancer cells. Cancer Sci. 2023;114(6):2460–2470. doi:10.1111/cas.15765.
26. Hao S, Sun S, Xiao X, He D, Liu L. Selective expression of transthyretin in subtypes of lung cancer. J Mol Histol. 2016;47(3):239–247. doi:10.1007/s10735-016-9666-3.
27. Zhu Y, et al. Effect and mechanism of transthyretin over-expression on proliferation and cell cycle of lung cancer A549 cells. Iran J Public Health. 2021.
28. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem 2023 update. Nucleic Acids Res. 2023;51(D1):D1373–D1380. doi:10.1093/nar/gkac956.