Exploring the Role of Network Pharmacology in Lung Cancer Treatment with Theaflavin-Derived Zinc Nanoparticles

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ABSTRACT

Introduction: Lung cancer remains one of the leading causes of global cancer deaths due to tumor heterogeneity, systemic toxicity, and drug resistance. Conventional therapies face limits in specificity and recurrence, thus paving the way for complementary or innovative alternatives. Nanotechnology along with network pharmacology is such an approach. Theaflavin is a polyphenol found in black tea used as medicine for heart disease, cardiovascular diseases,obesity and cancer . when conjugated with zinc nanoparticles (TF-ZnNPs), ensures more adequate bioavailability and stability and targeted anticancer activity. Aim:To study the therapeutic capacity of the zinc nanoparticles of theaflavin in lung cancer using a network pharmacology-aided approach. Materials and Methods: Theaflavin structures were obtained from PubChem while their protein targets were predicted by SwissTargetPrediction. Lung cancer-associated genes were fetched from GeneCards and OMIM. The overlapping targets were represented via Venn diagrams. GO and KEGG pathway enrichment analysis was done using ShinyGO. The PPI networks were constructed with STRING and Cytoscape, with hub genes identified using cytoHubba. Molecular docking was done using AutoDock Vina for binding affinity validation and PyMOL for visualization. Results : Thirty-four overlapping targets were identified. PPI analysis showed TP53, AKT1, EGFR, and MAPK1 as hub genes. GO analysis involved pathways of apoptosis, oxidative stress, and proliferation. KEGG enrichment analysis highlighted PI3K-Akt, MAPK, and Ras signaling. Molecular docking distinguished a strong binding of theaflavin with AKT1 and EGFR, supporting a multitarget-treated role. Conclusion: TF-ZnNPs increase tumor selectivity, solubility, and cellular uptake, offering a multitargeted strategy against lung cancer. These findings present great promise as a novel therapeutic approach, warranting further validation in in vitro and in vivo scenarios aimed toward clinical translation.

KEYWORDS: Lung cancer, Theaflavin-derived zinc nanoparticles, Network pharmacology , Nanotechnology in cancer therapy , Molecular docking and PI3K-Akt signaling pathways, cardiovascular diseases,obesity

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INTRODUCTION

Lung cancer is among the most fatal and aggressive malignancies globally , which accounts for nearly 1.8million deaths each year(1). The survival rates remain disappointingly low, despite significant advances in therapeutic and diagnostic interventions , especially in cases diagnosed at metastatic and advanced stages. Depending on various multifactorial pathogenesis the complexity of lung cancer varies, which involves epigenetic changes, genetic mutation , dysregulated signaling pathways, and intricate interactions within the tumor microenvironment(2). This biological heterogeneity contributes to high recurrence rate, disease progression and poor response to conventional therapies . Lung cancer is broadly classified into small cell lung cancer (SCLC) and non - small cell lung cancer (NSCLC), with non - small cell lung cancer accounting for the majority of cases(3). There are some conventional treatment regimes like chemotherapy, radiotherapy, including surgery and targeted therapies , which have limitations such as lack of specificity , systemic toxicity and the emergence of drug resistance (4)(5). Some additional mechanisms like immune evasion and intratumoral heterogeneity mechanism further complicate effective disease management (6). Since precision medicines continue to evolve. There is a need to explore some innovative treatment strategies that address the multifaceted biology of lung cancer . These emerging therapies are not only effective but also specific, safe and capable of overcoming existing treatment barriers. Due to this there is a growing interest in approaches such as network pharmacology and nano medicine(7).

The development of resistance to standard therapies is one of the major challenges in lung cancer. Cancer cells often mutate to avoid drug actions , which leads to reduced recurrence and efficacy. Some harmful side effects like immunosuppression, organ toxicity and gastro intestinal disturbance are caused due to radiotherapy and chemotherapy which often damage healthy tissues . Some targeted therapies , though more specific , are only effective in patients with some particular genetic mutations like anaplastic lymphoma kinase or Kirsten rat sarcoma viral oncogene homolo, epidermal growth factor receptor, which limits their broader applications(8). Lung cancer therapies also face some difficulty such as acquired resistance mechanisms in bypass signaling and in secondary mutations(9). Some immune therapies like immune checkpoint inhibitors have now revolutionized lung cancer care, where much of the patients don't respond to this therapy , where immune - related effects still remain in concern. Some plays a vital role in tumor resistance and progression one such is tumor environment which comprises immune cells, fibroblast and extracellular matrix, but current therapies often fail to target this dynamic niche effectively(10). Furthermore , short circulation times and poor drug availability further hamper treatment success. There is a need to explore alternative strategies , which target multiple biological processes and pathways simultaneously . To overcome these hurdles and enhance the precision and efficacy of treatment regimes , an integrating novel drug delivery system and systems biology tools into lung cancer therapeutics presents a promising avenue (10,11).

To overcome the limitations of traditional therapies , nanotechnology offers an innovative solution . Nanoparticles , due to their high surface area and small size, can be engineered for enhanced bioavailability, improved drug solubility and enhancing therapeutic efficacy. Ligands such as peptides or antibodies are targeted by functionalised nano carriers, enabling selective binding to tumor cells while sparing normal tissues . Among various nanomaterials such as dendrimers, liposomes, polymeric nanoparticles , due to their inherent multifunctionality and physicochemical properties, metal - based nanoparticles have shown particular promise(12). Due to their enhanced permeability and retention (EPR) , they can cross biological barriers, and accumulate preferentially in tumor tissues, and even exhibit intrinsic cytotoxic properties. Nanotechnology enables combination therapy approaches , allowing co - delivery of biological molecules and chemotherapeutic agents within a single platform(13). These properties make nanoparticles particularly well suited for complex diseases like lung cancer, Where multiple - targeted action is often necessary(11) . As the field progresses, nanomedicine is increasingly integrating with computational and omicron models, assuring a new era of precision oncology. Thus, nanotechnology represents pivotal advancements in modern pharmacology and in cancer care.

Due to some unique properties like reactive oxygen species (ROS), high biocompatibility and anticancer activity , zinc oxide nanoparticles (ZnONPs) have gained considerable attention in biomedical applications(14). These nanoparticles can induce oxidative stress in cancer cells, which leads to apoptosis while sparing healthy cells under controlled conditions. Zinc oxide nanoparticles possess surface chemistry and tunable size , which allows easy modification with therapeutic agents or targeting molecules (15). They also show strong potential for traversing barriers and penetrating biological membranes such as the blood - brain barrier, making them suitable for drug delivery in hard - to - reach tumors(16). Zinc oxide nanoparticles also offer mechanisms of action, including DNA fragmentation, mitochondrial dysfunction and disruption of cancer cell metabolism(17). To enhance efficacy and selectivity, their surface can be conjugated with bioactive compounds such as proteins or polyphenols. Additionally zinc oxide nanoparticles can be integrated into multifunctional nanocarriers or combination therapies, offering synergistic benefits(18). Their ability and safety profile to degrade into essential trace elements further support their use in therapeutic applications. Since there is a growing interest in metal - based nanoparticles like zinc - oxide nanoparticles reflect their potential to redefine cancer treatment, particularly when combined with system - level tools such as network pharmacology for mechanism - based drug development.

Theaflavin are a group of polyphenolic compounds . They are formed during the fermentation of black tea leaves, which are known for their anti - inflammatory, potent antioxidant and anticancer properties . There are four main types of theaflavins like TF1, TF2a, TF3b, and TF3 - posses varying number of gallate groups , with theaflavin - 3,3` - digallate being the most bioactive due to its dual galloyl groups. These structural features confer molecular binding potential and strong redox activity, allowing theoflavin to modulate multiple cellular signaling pathways(19)(20). Many studies have shown that theaflavins can inhibit induce apoptosis , tumor cell proliferation , suppress angiogenesis , and prevent metastasis in various cancer models. They also primarily affect pathways such as PI3K/AKT, NF - kB , MAPK/ERK and p53, which are crucial in lung cancer pathogenesis(21). The clinical applications of theaflavins is hindered by low bioavailability, poor solubility and limited stability in physiological conditions. To enhance therapeutic outcomes and to improve pharmacokinetics , researchers are exploring various delivery systems. Theaflavins thus represents a promising class of natural products whose potential can be amplified through advanced formulation strategies, paving the way for their incorporation into modern oncological treatments.

The development of theaflavin-conjugated zinc oxide nanoparticles (TF-ZnONFs) helps to overcome the limitations of free theaflavins . Theaflavin zinc oxide nanoparticles (TF-ZnONPs) demonstrate increased cellular uptake, controlled drug release and improved solubility ensuring reduced systemic toxicity and better tumor selectivity . These nanoparticles show superior cytotoxicity against lung cancer cells compared to their individual constituents (16)(18). Theaflavin zinc oxide nanoparticles are also an ideal candidate for investigating using network pharmacology. This made researchers analyze the complex interaction between pathways and multiple targets involved in lung cancer progression . By utilizing databases like STRING, TCMSP and gene cards, key signaling and potential protein target nodes can be validated and identified through pathway enrichment analyses and molecular docking . Omics data enhances the bridges and the accuracy of prediction of the gap between in vitro/in vivo studies and the silico models . Network pharmacology not only elucidates the mechanism of theaflavin zinc oxide nanoparticles but also aids in patients - specific applications and aids in identifying potential combination therapies,(18) positioning these nanocomposites as a cutting - edge advancement in targeted lung cancer therapy.

This research explores, Through the lens of network pharmacology the potential of theaflavins-derived zinc oxide nanoparticles in lung cancer therapy. By the physicochemical advantages of zinc oxide nanoparticles ZnONPs, TF-ZnONPs offer selectivity, efficacy and bioavailability. Network pharmacology aids in their complex molecular mechanism, identifying synergistic pathways and predicting drug - target interaction . This system-level approach supports the racial design of safer, more personalized nano therapeutics . The study aims to establish theaflavin zinc-oxide nanoparticles as a targeted, novel and effective strategy for addressing the challenges in lung cancer treatment.

MATERIALS AND METHODS :

From the PubChem database the 2D structure of Theaflavin was obtained in SDF format and subsequently converted into its conical SMILES representation . This format was submitted to Swiss Target Prediction platform http://www.swisstargetprediction.ch/ , which employ both 2D and 3D molecular similarity algorithms to predict potential human protein target for Theaflavin. As the functional cofactor zinc ions were incorporated in the formulation, aiming to enhance the therapeutic [potential and biological activity of theaflavin when developed into nanoparticles form . This approach supports more effective and targeted interactions with biological systems through metal-assisted pharmacological enhancement.

Disease - associated gene retrieval

Gene associated with lung cancer were comprehensively retrieved from two authorative biomedical databases - gene cards (https://www.genecards.org/) and OMIM (http://omim.org/) . USING THE KEYWORDS “non-small cell lung cancer”, “ lung adenocarcinoma” and “lung carcinoma”, an extensive search was conducted to identify relevant gene targets. From the resulting datasets, only genes with relevance scores were selected to ensure the clinical association and biological significance with lung cancer .

Venn Diagram Analysis of Overlapping Targets

To identify potential therapeutic targets, Through Venn diagram the protein targets of theaflavin were compared with lung cancer - associated genes. This was achieved using the online tool provided by the VIB bioinformatics core (http://bioinformatics.psb.ugent.be/webtools/Venn/) overlapping gene was obtained from this intersection represent common molecular element that are both affected by theaflavin and involved in lung cancer pathology .

Gene Ontology (GO) and KEGG Pathway Enrichment Analysis

The overlapping genes identified from venn analysis were uploaded in shinyGO v8.0 (http://bioinformatics.sdstate.edu/go/), a user-friendly platform for gene enrichment analysis. The tool was used to conduct gene ontology (GO) analysis across three main categories : molecular function, cellular component, and biological processes . Additionally , KEGG pathway enrichment was performed to identify critical signaling pathways involved in lung cancer. This include pathways related to metastasis , apoptosis , oxidative stress , inflammation and tumor growth. The analysis provided insights into the broader biological context and therapeutic relevance of Theaflavin-ZnNP interaction with these cancer related targets.

Protein - Protein Interaction (PPI) Network Construction

protein - protein interactions were conducted to investigate how the overlapping target gene interacts with the cellular environment **.** The common genes were submitted to the STRING database (https://string-db.org/), with a medium confidence threshold set at 0.4 to ensure reliability. The output interaction data were then imported in cytoscape software (version 3.9.1) for network analysis and visualisation . This PPI network thereby illustrating the systemic impact of Theaflavin - ZnNPs on lung cancer - related molecular pathways.

Hub Gene Identification

The most critical regulatory genes within the protein - protein interactions network , the cytoHubba plugin in cytoscape was employed . Based on maximal clique centrality (MCC) and degree the hubb genes were identified . The top 10 genes with highest scores were selected , as they likely play key roles in lung cancer development and progression . These hubb also represents crucial nodes in the network that could serve as therapeutic candidates or biomarkers candidates for targeted drug delivery and in cancer treatment.

Network Visualisation

To effectively illustrate the complex interaction among Theaflavin , its related signaling pathways and predicted gene gene targets, a compound - target - pathway network was constructed using cytoscape. In this network specific genes, nodes represented theaflavins and KEGG pathways , while edge depicted their interactions . The thickness of the edges corresponded to the confidence or strength level of the interactions, and the size of each node was adjusted based on its centrality or concavity within the network. It gives an overview of how Theaflavin - ZnNPs may influence multiple molecular pathways involved in lung cancer, supporting a multiple-targeted therapeutic approach.

To confirm and visualise the binding interactions between selected hub proteins and theaflavin the molecular docking studies were performed. From the RCSB Protein Data Bank (PDB) the 3D structure of the protein was retrieved. To ensure proper energy minimization and correct format conversion the ligand structures , including Theaflavin were prepared using open labels . The docking simulations were executed using AutoDock Vina, which calculates binding affinities and predicts the optimal binding poses. The resulting protein-ligand complexes were analyzed and visualized with PyMOL and discovery studio visualizer, which provides detailed insights into active site residues, binding interactions and molecular compatibility .

RESULTS

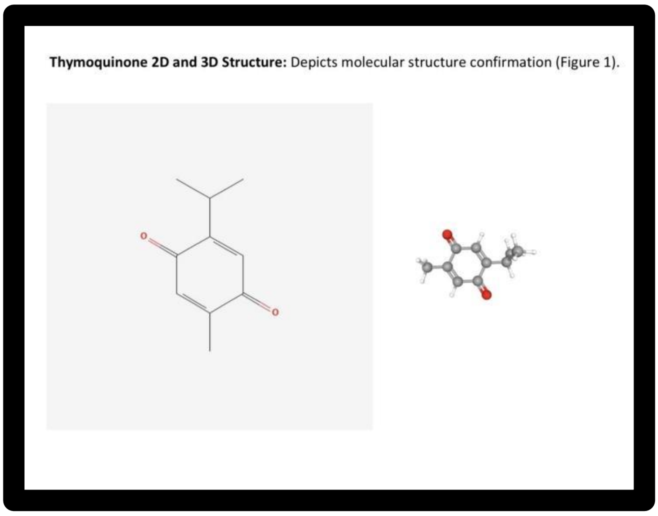

Figure1- illustrates 2D and 3D molecular structures of Thymoquinone, which confirms its configuration and chemical identity. The arrangement of functional groups , such as methyl and ketone substituents are highlighted by the 2D structure on the aromatic ring. The 3D structure provides spatial orientation, molecular geometry and showing bond angles, which are essential for understanding its biological interaction . This structural confirmation forms a crucial basis for further interactions studies and molecular docking , particularly in evaluating Thymoquinones therapeutic potential in disease models.

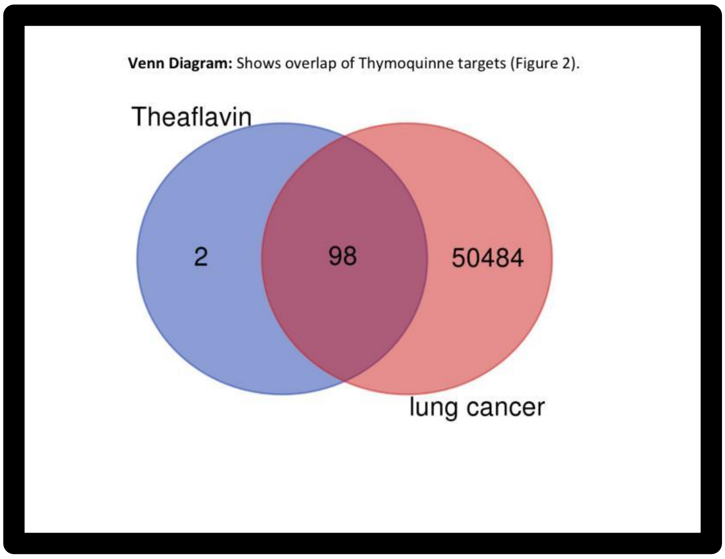

Figure 2- Illustration between Theaflavin - targeted genes and lung cancer - associated genes, identifying shared therapeutic targets was illustrated by this Venn diagram.

Target prediction of Theaflavin yielded 85 potential protein targets. Over 1500 genes , lung cancer - associated gene screening were identified, out of which 34 overlapped with theaflavins predicted targets. Venn Analysis verified these overlaps as key therapeutic candidates . These genes which was shared suggest that Theaflavin may modulate critical pathways involved in lung cancer progression offering potential for drug novel or repurposing therapeutic development.

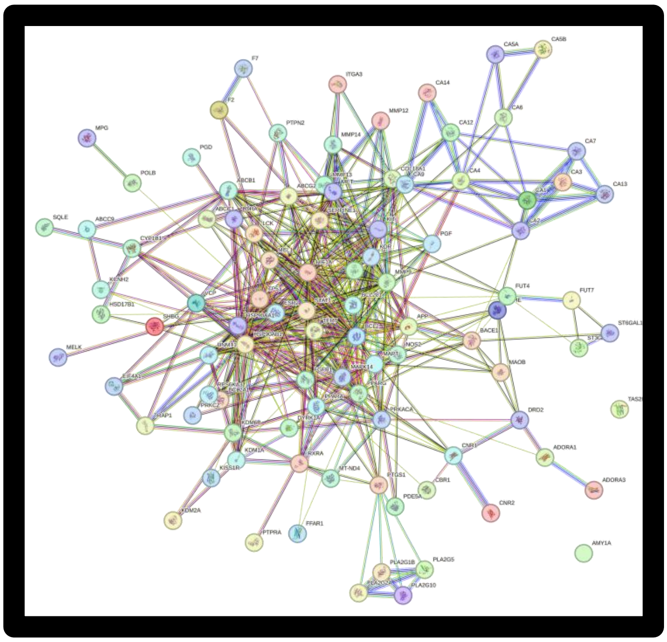

Figure 3 - The molecular targets associated with oral cancer were represented by a STRING - derived Protein - Protein interaction (PPI) network . The network provides insights into the intricate landscape among genes potentially involved in therapeutic response and disease progression. The STRING - derived protein - protein network (PPI) comprises of 112 edges and 34 nodes, which reveals multiple clusters of highly interconnected proteins.pathways such as NF-kB signaling, was notably analysed by this network, which plays a major role in immune regulation , tumor progression and in inflammation. Such enrichment helps in understanding the molecular basis and to identify potential targets for drug development of oral cancer pathology.

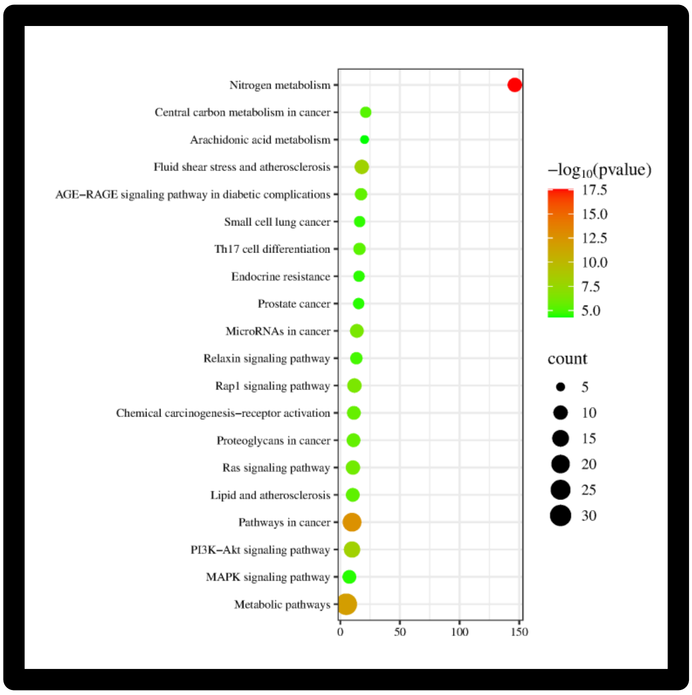

Figure 4 - Based on the analyzed gene set this bubble plot shows enriched KEGG pathways. Key cancer - related pathways , such as MAPK signaling, pathways in cancer and P13-AKT , are prominently represented, which indicates their role in disease progression. The top molecular function term includes DNA - binding transcription and including protein kinase activity, reflecting the involvement of transcriptional regulation and signal transduction in cancer biology . These enriched functions and pathways highlight potential molecular mechanisms through which the target genes influence survival, tumor development and metastasis, thereby offering insights into the therapeutic biomarker and targeting strategies identification in cancer treatment research.

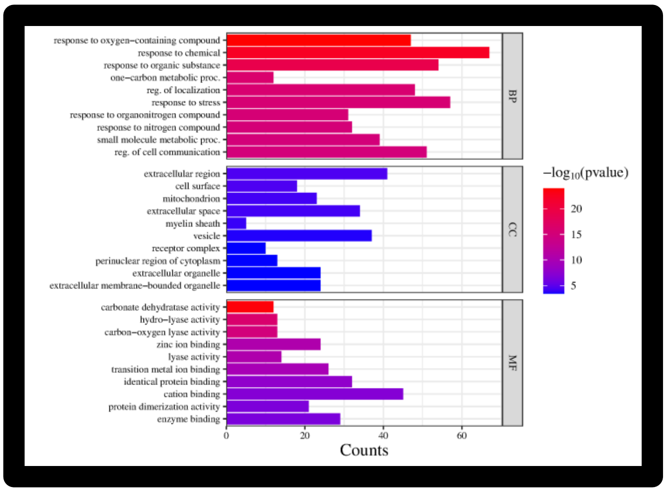

Figure 5 - Gene ontology (GO) enrichment analysis across three categories like : Biological processes (BP), cellular component (CC), and molecular function (MF) was represented by this bar chart.

The data highlights significant enrichment in pathways such as cell communication , chemical response and metabolic processes. Gene ontology (GO) analysis revealed that overlapping targets were primarily involved in regulation of oxidative stress response, cell proliferation and apoptotic processes, all of which are central to cancer progression. The visualisation also emphasises roles in the enzyme binding , extracellular region and metal ion interaction.

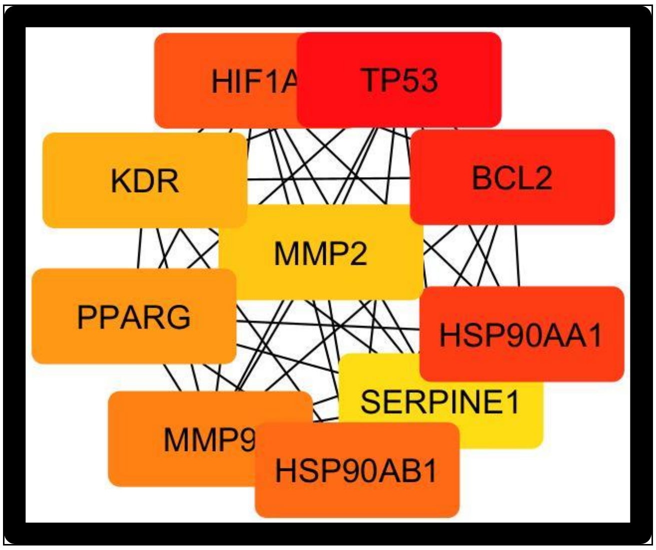

Figure 6 - Genes identified through CytoHubba analysis, were illustrated by the Key hub genes, which highlights their major role in the interaction network relevant to cancer biology.

Based on their connectivity the genes are colour coded , with TP53, HIF1A, BCL2, MMP2, and others showing high interaction density. CytoHubba analysis identified TP53, AKT1, EGFR, VEGFA and JUN as top hub genes. These genes are known as angiogenesis, regulators of tumor growth and apoptosis, making them critical targets for understanding potential therapy and cancer mechanisms . This visualisation emphasises the functional importance of these central genes in oral cancer regulation and progression.

DISCUSSION

This investigational research revolves around studying the lung cancer targeting activities of the aflavin-mediated zinc nanoparticles against NSCLC through network pharmacology and molecular docking. Theaflavin, a polyphenol from black tea, showed good binding affinities for two important oncogenic targets, AKT1 and EGFR (epidermal growth factor receptor), which serve as crucial regulators in tumorigenesis(22,23). Molecules were docked, and theaflavin interacted with the active sites on both proteins, hence could be considered as a multi-target therapeutic compound for drug development. EGFR takes part in cellular proliferation and metastases and also in resistance to chemotherapy, while AKT1 is centrally involved in the phosphoinositide 3 kinase (PI3K)/AKT signaling axis and is usually overexpressed in lung cancer(22). The binding of theaflavin to these targets further indicates the potential ability to inhibit various pathways leading to malignancy, and consequently, the possible further development of clinical therapies.

The combination of zinc nanoparticles and theaflavin thus addresses one of the main limitations of traditional phytochemicals: poor bioavailability. Natural flavonoids such as theaflavin are endowed with a grand spectrum of biological activities; however, they suffer from poor water solubility, rapid metabolism, and inadequate tissue distribution that limit their therapeutic effect. Conjugation to zinc-based nanoparticles increases the water solubility, stability to degradation, and cell internalization of theaflavin, thereby presumably increasing its activity(24). Besides contributing zinc as an essential trace element for various cellular processes, it acts as an anticancer stress factor inducing oxidative stress and apoptosis in cancer cells. Afterward, these nanoparticles promote targeted delivery through endocytosis and other processes to ensure the drug agent is delivered effectively to the tumor site while restraining its off-target side effects(25). Reformulations aided by nanotechnology are examples of how nanotechnology tackles pharmacological barriers to translate a naturally occurring molecule into a drug candidate.

The KEGG pathway enrichment analysis reveals that theaflavin-zinc nanoparticles act on major oncogenic signaling pathways, primarily the PI3K-AKT and MAPK pathways(26). These two pathways are heavily implicated in cellular processes of proliferation, differentiation, angiogenesis, as well as survival. In cancer, especially in NSCLC, these signaling cascades tend to be constitutively activated and promote unrestrained growth and resistance to therapy methods. Theaflavin probably targets these pathways to induce apoptosis and inhibit tumor progression. Besides, such nanoparticulate formulations provide better interactions with intracellular targets to maintain sustained inhibition of these pathways and hence curb tumor progression, giving an even greater anti-tumor effect, which has been affirmed further by a series of in vitro studies of flavonoid-nanoparticles inducing more death of cancer cells, less colony formation, and inhibition of metastasis when compared to free flavonoids.

The study offers a strong basis for further experimental research, predominantly focusing on the validation of the suggested molecular interactions through in vitro and in vivo assays. Further investigations would solidify the mechanism of action for the aflavin-zinc nanoparticles with respect to their capability to generate ROS, induce mitochondrial dysfunction, and hence, activate caspase-mediated apoptosis(27). Cytotoxicity assays against normal versus cancer cells, tumor regression studies in animal models, and potential synergy with current chemotherapies should be conducted. Another opportunity with nanoparticle formulations proves to be in personalized medicine, where surfaces could be modified for particular tumor markers or to co-deliver multiple agents. Marrying system-level computational approaches with experimental validation, theaflavin-zinc nanoparticles promise to be the next-generation therapeutic agents for treating lung cancer.

CONCLUSION

Therefore, GO enrichment is useful in implicating biological processes, cellular components, and molecular functions that potentially bear on the overlapping targets. These were mainly related to regulation of oxidative stress, cellular response to chemical stimuli, and apoptosis, and hence are very central into cancer development and progression. On the other hand, metal ion binding and extracellular localizations could suggest other pathways through which TF-ZnNPs exert their effects, specifically through membrane-associated interactions and signaling cascades.

The KEGG pathway analysis then placed emphasis on several signal routes of importance, namely, PI3K-Akt, MAPK, and Ras. These have been well characterized to be instrumental for lung cancer tumorigenesis, metastasis, and therapeutic resistance. Enrichment of these pathways argued further for the multifaceted action of TF-ZnNPs and therefore raised the level of anticipation regarding how these nanoparticles might be acting to disrupt tumor-promoting signaling networks at multiple checkpoints.

From a cumulative standpoint, these results describe zinc nanoparticles derived from theaflavin as broad-spectrum multitarget actors consistent with the theory of network pharmacology advocating overall and systems-based drug interaction. By hitting genes and pathways related to cancer simultaneously, TF-ZnNPs hold the promise not just as anticancer agents but also as tools for combination therapies or drug delivery with nanocarriers for lung cancer.

Hence, the study shows the realization of considering computational and biological networks to decipher therapeutic relevance on the scale of nature-derived nanomaterials, suggesting media for the highly promising treatment of lung cancer through TF-ZnNPs acting upon multiple oncogenic pathways, as indicated by rigorous bioinformatics and molecular interaction analyses. Further experimental validations must include in vitro and in vivo studies to turn these findings into real clinical treatment in the near future and investigate their anti-cancer potential within a precision oncology environment.

CONFLICT OF INTEREST

The authors hereby declare that there is no conflict of interest in this study.

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