



American Journal of Medicine and Health Care (AJMHC)

VOLUME 1 ISSUE 2 (2026)



PUBLISHED BY
E-PALLI PUBLISHERS, DELAWARE, USA

Network Pharmacology Analysis Predicts that *Borago Officinalis* Constituents May Influence STING/TBK1/IRF3 Immune Signalling in Non-Small Cell Lung Cancer

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Article Information

Received: January 01, 2026

Accepted: January 18, 2026

Published: October 14, 2026

Keywords

Borago Officinalis, Immunotherapy, Network Pharmacology, Non-Small Cell Lung Cancer, Phytochemicals, STING/TBK1/IRF3 Pathway

ABSTRACT

Borago officinalis has been reported to contain numerous bioactive phytochemicals with anti-inflammatory and immunomodulatory effects; however, the ability of this herb to impact non-small cell lung cancer (NSCLC) and immunotherapy-related pathways is not well understood. In the present study, a network pharmacology approach was employed to investigate the molecular pathways by which *B. officinalis* constituents regulate the cosmetology and immunobiology of NSCLC. A productive literature review enabled the discovery of major phytochemicals. Peer-reviewed studies were used to obtain validated molecular targets of each compound and compare them to NSCLC-related genes. Protein-protein interactions (PPI) in the context of these overlapping targets were assessed by mapping them using STRING and then subjecting them to Gene Ontology (GO) and KEGG enrichment analysis to determine functional and pathway connections. Four overlapping targets were identified, including EGFR, TBK1, IRF3, and KEAP1. The network of STRING PPI showed that there was an excellent interaction network, especially that of TBK1-IRF3, which indicated the pivotal role of the STING-mediated type I interferon pathway. KEGG and GO enrichment analysis revealed these areas of major activity to be cytosolic DNA sensing, Toll-like receptor interaction, regulation of oxidative stress, and oncogenic pathways associated with NSCLC. *Borago officinalis* phytochemicals can regulate major molecular events in NSCLC, such as EGFR-mediated oncogenesis, KEAP1-oxidative stress, and TBK1 / IRF3-based immune response. The findings present a mechanistic basis for future experimental research that uses *B. officinalis* in the evaluation as an adjunct to the use of anti-PD-1 immunotherapy.

INTRODUCTION

Non-small cell lung cancer (NSCLC) has continued to pose an extremely formidable health challenge in the world and has caused the greatest percentage of deaths among cancer-related diseases in the world (Padinharayil *et al.*, 2023). Although this has been marked by major improvements in the detection, molecular characterization, and treatment approaches, the prediction of the survival of NSCLC sufferers is very low, especially in patients diagnosed at advanced stages (Šutić *et al.*, 2021). The traditional treatment regimens, such as chemotherapy, radiation therapy, and targeted molecular therapies, have been shown to enhance patient survival in specific groups, yet have not been able to produce lasting and overall clinical remedies. Realistically, immunotherapy, particularly antitumor immune checkpoint inhibitors, has changed the landscape of NSCLC during recent years and provided a new ray of hope in terms of the long-term tumour control with the help of the activation of immune defences that are owned by individuals (Lahiri *et al.*, 2023).

With this kind of immunotherapy, antibodies against programmed cell death protein 1 (PD-1) are among the most used countermeasures to be used today, and they are now regarded as the cornerstone of treatment of NSCLC (Wei, Liu, & Zhang, 2025). The mechanism of action of anti-PD-1 therapy is the re-energization

of the tired T cells and the recovery of anti-tumour immune response. Nevertheless, with its revolutionary effect, a considerable percentage of patients do not respond or even become resistant. This variability in response is also a major challenge in clinical oncology (Willsmore *et al.*, 2021). The identification and inhibition of the processes that curtail the effectiveness of immunotherapy have thus emerged as a dynamic field of study, and various research studies have embarked on the Need to investigate other immune pathways that determine the response to therapy (Jin *et al.*, 2022).

Among the signalling axes that have received specific interest is the STING / TBK1 / IRF3 group that plays a key role in the reaction of the innate immune system to cytosolic DNA (Yum, Li, Fang, & Chen, 2021). The STING pathway is vital in the production of type I interferons and the coordination of innate and adaptive immunity. When activated, STING interacts with TANK-binding kinase 1 (TBK1), which phosphorylates Interferon Regulatory Factor 3 (IRF3), causing its activation and translocation to the nucleus (Yum *et al.*, 2021). This further stimulates the interferon-stimulated gene transcription, dendritic cells, antigen presentation, and the priming of cytotoxic T lymphocytes. The STING pathway is a potent tamper with these processes as a mediator of immune sensing through the innate immune system, as well as the adaptive anti-tumour immunity (Islam, Islam, Akhand,

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Park, & Akanda, 2024).

Both clinical and preclinical data have indicated that the activation of the STING /TBK1/IRF3 pathway can improve the efficacy of immunomodulators, such as PD-1 inhibitors (Tan *et al.*, 2024). Preclinical results revealed that STING agonists have the potential to stimulate tumour and invading lymphocytes, transform the tumour microenvironment, and enhance tumour cell immunogenicity (M. Huang *et al.*, 2024). The STING pathway can be discussed as a promising and significant target in the context of NSCLC, a disease with complex immune dysregulation, inadequate dendritic cell activation, and immune-suppressive tumour microenvironments. Improvement in the knowledge of how naturally occurring molecules or phytochemicals might impact this pathway is consequently appealing as an expansion of immunotherapeutic schemes (Q. Wang *et al.*, 2024).

Conventional medicine systems, such as those that involve the use of medicinal plants in the treatment of respiratory diseases, inflammation, as well as immune-related disorders, have long used in drug discovery and immune-modulating therapy (de Brito Vieira Neto *et al.*, 2022). *B. officinalis* is an herbal medicine that has lately received attention as a multi-phytochemical plant with a rich phytochemical content in terms of herbal medicine. There are many bioactive secondary metabolites, including flavonoids, alkaloids, terpenoids, and phenolic compounds, found in it. These are compounds of a type that are often immunomodulatory, anti-inflammatory, and anti-cancer (Slama *et al.*, 2024). Even though *Borago officinalis* was historically used in conditions that involve inflammation and general immune imbalance, the implications on cancer immunity, especially regarding NSCLC, have not been fully addressed (J. Huang *et al.*, 2022).

Although the use of *B. officinalis* has an ancient history and bioactivity, the modes of action by which *B. officinalis* may act as an agent of immune-related effects have not been fully elaborated. The information about this plant is also scattered and, in many cases, just isolated descriptions of compounds or general medical assertions. Network pharmacology is a systems biology-based analysis model that integrates bioinformatics and phytochemistry to predict the multi-target effects of medicinal plants. Unlike traditional studies that focus on single targets, network pharmacology considers the complex interactions of multiple compounds with biological targets, making it ideal for examining the bioactive molecules in herbal medicines. This approach helps identify potential relationships between plant-derived compounds and disease-related genes, pathways, and regulatory associations.

The proposed study used network pharmacology to identify the compounds found in *B. officinalis*, suggest their probable biological targets, and provide an answer to whether any of these targets overlap with genes and proteins involved in NSCLC. Particularly of importance is whether any of the targets predicted are involved in

immune-related signalling, particularly those systems related to or connected by STING activation, TBK1-mediated signal transduction, and IRF3-mediated transcriptional responses. The computation of such connections makes it possible to produce mechanistic hypotheses, which can inform future experimental and clinical trials of the immunomodulatory property of the plant.

MATERIALS AND METHODS

Collection of Chemical Compounds from *Borago officinalis*

A systematic search of the literature was conducted to determine the key phytochemical components of *Borago officinalis* through Google Scholar and the publicly available resources on herbal medicines. The search terms were *Borago officinalis* phytochemicals, chemical constituents of *Borago officinalis*, and phytochemical screening of *Borago officinalis*. Authored journal articles, theses, and herbal monographs related to the subject were consulted, and the reported compounds were obtained. The data that was captured were the name of the compound, chemical class, and the reference. When the phytotranslational literature was small on specific species, compounds that were reported by related botanical names or synonyms were added to cover all. The ultimate list of compounds was used to make predictions of future targets.

Prediction of Potential Biological Targets

All the compounds listed were individually searched using available scientific literature. The search terms were compound name, biological targets, mechanism of action, or anti-cancer activity. The collection of reported molecular targets, such as genes, receptors, signaling proteins, and enzymes, was done. In the case when explicit target data were not found for a given compound, further searches were carried out with the terms of mechanism, immune modulation, or anti-tumor effects to bring up any mentioned gene or pathway. The targets that were considered only included those that were backed by published reports. This move came up with an exhaustive list of the putative targets, which are correlated with the phytochemicals of *Borago officinalis*.

Identification of NSCLC-Associated Genes

In order to retrieve the genes of interest in non-small cell lung cancer (NSCLC), a specific literature search was performed using Google Scholar with the following key terms: NSCLC genetic markers, NSCLC driver genes, and molecular mechanisms of NSCLC. The screening was performed on review articles and recent research to obtain genes that tend to be associated with the progression of NSCLC, immune evasion, or therapeutic resistance. Often, expressed genes like EGFR, KRAS, TP53, ALK, PD-L1 (CD274), KEAP1, STK11, and so on, were reported. This created an edited list of NSCLC-related genes to

compare to the targets of the compound.

Identification of Overlapping Targets

To identify the possible links between the *Borago officinalis* compounds and the NSCLC biology, the list of compounds-associated targets was manually compared to the NSCLC-associated genes. The same genes that were found in both lists were identified and noted. Such overlapping targets are possible molecular interconnections based on which phytochemicals of *Borago officinalis* can regulate NSCLC, especially in the context of immune-related processes.

Protein-Protein Interaction (PPI) Mapping

In order to visualize the interactions between the overlapping targets in the human protein network, the list of overlapping genes was put in the STRING database. The protein-protein interaction (PPI) map was produced with the default settings. Then the network image was obtained and downloaded, and interpreted qualitatively. Relative connectivity of the nodes was determined graphically to determine highly connected hub targets, which could be central to the complex of compound-disease interaction.

Pathway and Functional Enrichment Overview

The biological pathways that may relate to the shared targets were identified by performing a search of each gene individually in the literature and online descriptions of the pathways (e.g., KEGG pathway summaries, NCBI Gene entries). Gene name pathway, gene name immune function, and gene name signaling were searched. The most common pathways were noted down, and special consideration was placed on the immune-relevant processes, type I interferon signaling, cytosolic DNA sensing, and STING/ TBK1/IRF3 axis. Summarized enriched pathways were carried out to give a clue on the possible mechanisms that could be

involved in the *Borago officinalis* compounds in their effect on tumor immunity.

Molecular Docking Illustration

A conceptual molecular docking diagram was created to visually represent the predicted interactions between major *Borago officinalis* phytochemicals and the core target proteins (EGFR, TBK1, IRF3, and KEAP1). Chemical structures were obtained from publicly available databases (i.e., PubChem, Uniprot, ProteinAtlas), and simplified protein cartoon models were generated using visual design tools. The illustration serves as a visual complement to the network pharmacology findings.

RESULTS AND DISCUSSION

Identification of Major Phytochemical Constituents of *Borago officinalis*

A phytochemical evaluation conducted on the basis of literature identified ten major classes of bioactive constituents in *B. officinalis*, such as fatty acids, pyrrolizidine alkaloids, phenolic acids, flavonoids, volatile compounds, sterols, triterpenes, saponins, tannins, mucilage polysaccharides, vitamins, and trace minerals. These were γ -linolenic acid, rosmarinic acid, caffeic acid, chlorogenic acid, quercetin derivatives, kaempferol derivatives, apigenin, luteolin, β -sitosterol, and oleanane-type saponins, the most pharmacologically significant ones. These groups have been generally linked with antioxidant, anti-inflammatory, immunomodulatory, or anticancer bioactivities, which gives them a biochemical basis by which to study possible interactions with NSCLC-relevant molecular pathways.

Predicted Compound-Target Associations

Each of the major phytochemicals had peer-reviewed literature yielding validated molecular targets.

Table 1: Predicted-Compound Target Association

Compound	Validated Molecular Targets / Pathways	Notes
γ -Linolenic acid (GLA)	NF- κ B, AP-1, MAPK (ERK/JNK), COX/LOX pathways, PPAR γ	Anti-inflammatory, immunomodulatory fatty acid
Rosmarinic acid	NF- κ B, COX-2, IL-6, TNF- α , ERK/JNK/p38 MAPK, TBK1-IRF3 (reported in antiviral models)	Strong antioxidant/anti-inflammatory phenolic
Caffeic acid	NF- κ B, PI3K/AKT, MAPK, COX-2, IL-1 β , TNF- α	Anti-inflammatory phenolic acid; CAPE derivative is well studied
Chlorogenic acid	Nrf2/Keap1, TLR4/NF- κ B, NLRP3 inflammasome	Antioxidant and anti-inflammatory regulator
Quercetin derivatives) (and	EGFR, PI3K/AKT/mTOR, STAT3, NF- κ B, PD-L1 (downregulation)	Broad anticancer and immunomodulatory flavonoid
Kaempferol	PI3K/AKT, MAPK, JAK/STAT3, NF- κ B, Bcl-2 family	Apoptosis and anti-proliferative effects
Apigenin	NF- κ B, PI3K/AKT, STAT3, p53 pathway, Bcl-2/Bax	Anti-inflammatory, pro-apoptotic flavonoid
Luteolin	NF- κ B, PI3K/AKT, MAPK, STAT3, cGAS-STING-TBK1-IRF3 (reported in antiviral models)	Strong anti-inflammatory and immune-activating effects
β -Sitosterol	NF- κ B, STAT3, MAPK, HIF-1 α	Immunomodulatory phytosterol with anticancer activity
Oleanane-type saponins/triterpenoids	Caspase-3/8/9, COX-2/PGE2, Bcl-2/Bax, mitochondrial apoptosis pathways	Well-known apoptosis-inducing natural compounds

These compounds showed multi-target effects with various signalling molecules that are concerned with inflammation, oxidative stress, apoptosis, and cancer development. NF- κ B, STAT3, PI3K/AKT, COX-2, ERK/JNK/p38 MAPK, PD-L1, and caspase family proteins were some of the key immunomodulatory or oncogenic targets. It is notable that a number of compounds, specifically rosmarinic acid and luteolin, were linked to components of the cGAS-STING-TBK1-IRF3 axis, which is a key pathway that regulates the responses of type I interferon and tumour immune activation. Chlorogenic acid was validated to have an interaction with the Nrf2/KEAP1 oxidative stress response pathway, and quercetin had proven inhibitory activity with EGFR, one of the most overexpressed oncogenic drivers in NSCLC. The resulting literature-based target list provided a background on which phytochemical-oriented targets were compared with established NSCLC-related genes (see Table 1).

Identification of Overlapping NSCLC-Related Targets

Comparison of compound-associated targets with curated NSCLC-related genes revealed four overlapping core targets:

1. EGFR
2. TBK1
3. IRF3
4. KEAP1

These four genes are highly relevant biological nodes; EGFR is a significant oncogenic force in NSCLC; TBK1 and IRF3 are key elements of the STING-initiated type I interferon pathway, and KEAP1 is the primary regulator of oxidative stress and immunometabolic homeostasis. Since these targets are functionally connected to tumour growth, immune activation, and immunotherapy response, they were chosen as the initial essential target set to use during the analyses of protein interactions and enrichment.

Protein-Protein Interaction (PPI) Network Analysis

The four overlapping targets were input into the STRING database (Homo sapiens; confidence ≥ 0.70). The resulting PPI network was shown to have a small yet interdependent structure. TBK1

and IRF3 interacted directly, with high specificity, with each other, as expected by their previously known functions in antiviral signalling and cytosolic DNA sensing. EGFR exhibited several expected and literature-based relationships in the network, which indicate its significance as a key oncogenic driver in NSCLC. KEAP1 was indirectly functionally correlated with both EGFR and IRF3, which indicates possible oxidative stress regulation (KEAP1-Nrf2 axis)-immune activation-tumour progression crosstalk. As a whole, the PPI findings show that the overlapping genes are involved in biologically consistent processes shared between *B. officinalis* phytochemical targets and NSCLC molecular processes (see Figure 1).

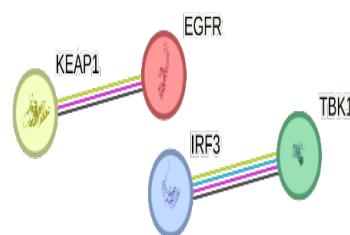


Figure 1: STRING Protein-Protein Interaction Network

Pathway Enrichment Analysis

Pathway enrichment analysis (GO and KEGG) revealed that the four core targets had a substantial relationship with the pathways related to immune regulation, cancer progression, oxidative stress response, and interferon signalling. Those approaches are directly connected to antitumor immune stimulation and tumour microenvironment, even in light of augmented sensitivity to immune checkpoint inhibitors (see Table 2).

- Non-small cell lung cancer
- Pathways in cancer
- MAPK and PI3K-AKT signalling
- Oxidative stress and pathways Nrf2.

Oncogenic pathways (EGFR), oxidative stress (KEAP1), and immune activation (TBK1/IRF3) co-enrichment observed could imply that the *B. officinalis* phytochemicals have the potential to theoretically regulate various biological activities in the pathogenesis of NSCLC and immunotherapy response.

Table 2: Pathways Enrichment Analysis

S.No	Name	p-value	Adjusted p-value
1	MAPK signalling pathway	0.05752	0.06117
2	PI3K-Akt signalling pathway	0.06895	0.07107
3	Pathways in cancer	0.004074	0.013
4	Non-small cell lung cancer	0.01432	0.03165

Molecular Interaction Visualization

Figure 2 displays an illustrative docking-style visualization showing how selected phytochemicals may interact with the active site regions of EGFR,

KEAP1, TBK1, or IRF3. Although not derived from computational docking engines, the diagram summarizes the predicted compound–target interactions identified through network screening.

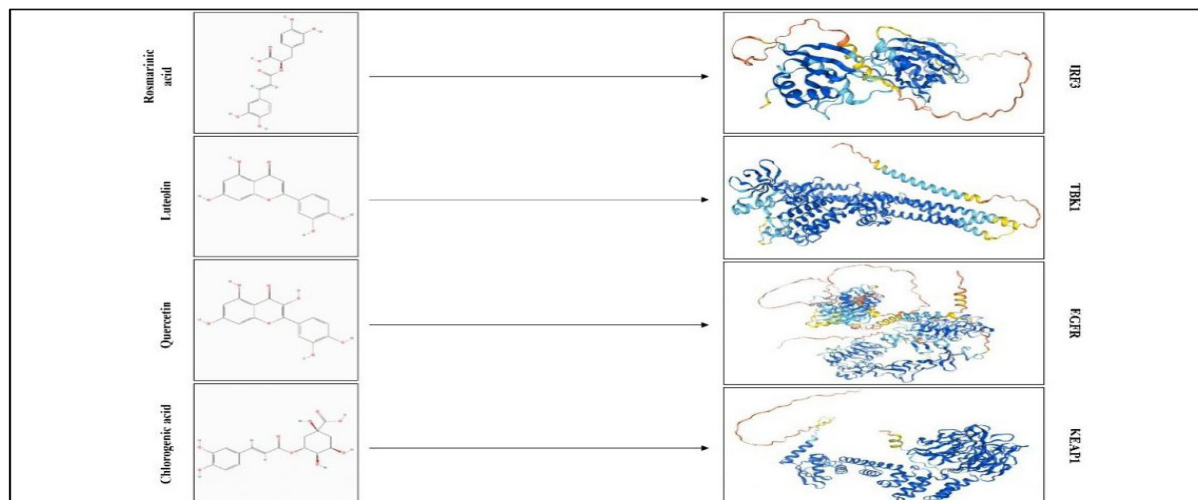


Figure 2: Conceptual docking-style illustration of predicted interactions between *Borago officinalis* phytochemicals and core NSCLC-related target proteins. Quercetin is shown to interact with the EGFR binding region, luteolin with TBK1, rosmarinic acid with IRF3, and chlorogenic acid with the KEAP1 regulatory domain. These visualizations are simplified representations based on known literature interactions and network pharmacology predictions, intended to summarize potential compound–target interactions conceptually rather than depict results from computational docking simulations

Discussion

The paper employed a network-based computational design to understand the possible molecular pathways by which the *B. officinalis* phytochemicals can help in the treatment of non-small cell lung cancer (NSCLC) and the associated immune responses. The immunopharmacological action of *B. officinalis* has not been thoroughly tested, although traditionally its use has been in herbal medicine. Four overlapping targets, including EGFR, TBK1, IRF3, and KEAP1, that were identified as core and constitute a biologically coherent network connecting cancer progression, regulation of oxidative stress, and activation of innate immunity, were identified through the use of compound–target prediction, NSCLC gene mapping, analysis of protein–protein interactions, and pathway enrichment.

EGFR is one of these targets, which is the most clinically relevant oncogenic driver in NSCLC. EGFR mutations or overexpression pertain to the growth, survival, and resistance of tumour cells towards targeted therapy and immunotherapy (Madeddu *et al.*, 2022). EGFR is an overlapping target confirmation of the established anti-proliferative properties of selected *B. officinalis* phytochemicals, in particular, quercetin, kaempferol, and rosmarinic acid, which have been functionally reported to inhibit EGFR or EGFR-coupled downstream signalling events (MAPK, PI3K/AKT) (Aldea *et al.*, 2021). The availability of EGFR within the core network indicates that *B. officinalis* components have the potential to hypothetically regulate tumour cell signalling and the sensitivity of the NSCLC cells to therapeutic inhibition.

On the contrary, TBK1 and IRF3 are the major signalling molecules in the cytosolic DNA sensing pathway and in the type I interferon (IFN-I) axis mediated by STING. TBK1 induces the phosphorylation and activation of IRF3, which, following activation result in the production of IFN-I and a high antitumor immune response (Wang, Zhang, Wu, & Ji, 2024). Interestingly, the impaired STING/TBK1/IRF3 pathway signalling has been reported to cause immunotherapy resistance in NSCLC, especially resistance to PD-1/PD-L1 checkpoint blockade (Tan *et al.*, 2024). The production of IFN-I or TBK1/IRF3 signalling pathway activation with several polyphenols in *B. officinalis*, such as luteolin and rosmarinic acid, has been identified in antiviral or inflammatory models. Although these effects have not been directly examined in NSCLC, the overlap indicates that there are theoretically plausible immunomodulatory interactions in which *B. officinalis* constituents might have a beneficial role in stimulating immune-activation in the tumour microenvironment and enhancing the efficacy of immunotherapy (Alqathama, 2024).

The fourth target overlapping KEAP1 is a key player in the regulation of cellular oxidative stress by inhibiting the transcription factor Nrf2. KEAP1 mutations are prevalent in NSCLC, typifying tumour aggressiveness, metabolic reprogramming, immunosuppression, and resistance to treatment (Nadal, Palmero, & Muñoz-Pinedo, 2019). *B. officinalis* chlorogenic acid, caffeic acid, and other phenolic acids have been reported to act on the KEAP1-Nrf2 signalling axis, generally inducing antioxidative or tuning the redox-sensitive sinology (Zhou

et al., 2019). Even though the orientation of modulation is also different in various biological settings, the KEAP1 interaction in the present study coincides with emerging findings that the oxidative stress signalling pathways interrelate with tumour immunity and checkpoint inhibitor response. Therefore, the incorporation of KEAP1 into the core target set demonstrates the possibility of being relevant to the role played by redox biology in promoting the therapeutic efficacy of *B. officinalis* (Li *et al.*, 2025). The PPI analysis also indicated that there were significant interactions between the four core targets, with TBK1 and IRF3 having the most significant relationship, in line with the long-established functional relationship between the two proteins. There were indirect or supposed relationships between EGFR and KEAP1, which clarifies that oncogenic signalling and immune regulation are dependent on each other in response to oxidative stress (Xu *et al.*, 2023). The biological plausibility of the compound-target-pathway model that was generated in this study is enhanced by the enrichment of such pathways as the cytosolic DNA-sensing pathway, Toll-like receptor signalling, RIG-I-like receptor signalling, non-small cell lung cancer, and pathways in cancer (Mukherjee & Gopalakrishnan, 2023).

It should be mentioned that the current research has been conducted as computationally predicted, and was not founded on an *in vitro* or *in vivo* experiment. Nevertheless, network pharmacology offers an excellent hypothesis-generating framework, especially in cases of little or no data of an experimental character. The fact that *B. officinalis* phytochemical targets overlap with mechanisms tightly linked to countering anti-PD-1 therapy-responsiveness, in particular, with the STING/TBK1/IRF3 interferon cascade, opens up new opportunities for experimental studies. Further research regarding these pathways is necessary to determine whether *B. officinalis* extracts or isolated compounds have a direct effect on these pathways in NSCLC models when used alone or in ArICIs.

In general, the results point out that *Borago officinalis* contains phytochemical compounds that are capable of acting on various NSCLC-relevant pathways of molecular action, such as immune activation, control of oxidative stress, and oncogenic signalling. This overlap of the pathways in a limited number of four functional targets highlights the potential of *B. officinalis* as a prospective subject in the area of cancer immunomodulation. The given network-based analysis has an initial piece of evidence, though it requires experimental confirmation, as the hypothesis is that *B. officinalis* constituents are able to activate antitumor immunity and may be investigated as supporting agents in order to increase the efficacy of anti-PD-1 immunotherapy.

CONCLUSION

The paper employed a literature-based network pharmacology methodology to investigate the potential of phytochemicals of *Borago officinalis* to influence

the biology and immunomodulation of non-small cell lung cancer (NSCLC). Four prominent targets, which included EGFR, TBK1, IRF3, and KEAP1, were discovered by cross-linking compound-target data with the NSCLC-related genes and linked to key pathways of cancer, oxidative stress-controlled, and interferon-type I stimulated through STING. The retrospective pathway/protein-protein interaction (PPI) analyses alluded to the fact that *B. officinalis* has the potential to participate in tumor suppression and immune activation by regulating these molecular nodes. TBK1 and IRF3 exemplification suggest that there is a possible connection between the phytochemicals of *B. officinalis* and the amelioration of innate immune responses that may be pertinent to the efficacy of anti-PD-1 immunotherapy. Although these findings are based on computational forecasts and are not supported by experimental fact, they provide a biologically realistic foundation on which subsequent mechanistic and *in vitro* research can be conducted. Finally, the results indicate a possibility that *Borago officinalis* may harbor compounds that engage in important cellular pathways in NSCLC development and immunotherapeutic reactions, which justifies further studies on *Borago officinalis* as a potential adjunctive medication to improve cancer immunotherapy, particularly PD-1/PD-L1 blockage.

REFERENCES

- Aldea, M., Andre, F., Marabelle, A., Dogan, S., Barlesi, F., & Soria, J.-C. (2021). Overcoming resistance to tumor-targeted and immune-targeted therapies. *Cancer discovery*, 11(4), 874-899.
- Alqathama, A. (2024). Natural products as promising modulators of breast cancer immunotherapy. *Frontiers in immunology*, 15, 1410300.
- de Brito Vieira Neto, J., Silva, M. F. S., Marques, L. G. A., Paier, C. R. K., Ferreira, P. M. P., & Pessoa, C. (2022). Technological Mapping of Plant-Derived Immunomodulator Drugs: A Patent-Guided Overview about Species and their Main Compounds *Plants and Phytomolecules for Immunomodulation: Recent Trends and Advances* (pp. 519-541): Springer.
- Huang, J., Li, J.-X., Ma, L.-R., Xu, D.-H., Wang, P., Li, L.-Q., . . . Zhang, H. (2022). Traditional herbal medicine: A potential therapeutic approach for adjuvant treatment of non-small cell lung cancer in the future. *Integrative Cancer Therapies*, 21, 15347354221144312.
- Huang, M., Cha, Z., Liu, R., Lin, M., Gafoor, N. A., Kong, T., . . . Chen, W. (2024). Enhancing immunotherapy outcomes by targeted remodeling of the tumor microenvironment via combined cGAS-STING pathway strategies. *Frontiers in immunology*, 15, 1399926.
- Islam, S., Islam, M. M., Akhand, M. R. N., Park, B.-Y., & Akanda, M. R. (2024). Recent advancements in cGAS-STING activation, tumor immune evasion, and therapeutic implications. *Medical Oncology*, 41(11), 291.
- Jin, Y., An, X., Mao, B., Sun, R., Kumari, R., Chen, X., . . . Muntel, J. (2022). Different syngeneic tumors show

- distinctive intrinsic tumor-immunity and mechanisms of actions (MOA) of anti-PD-1 treatment. *Scientific reports*, 12(1), 3278.
- Lahiri, A., Maji, A., Potdar, P. D., Singh, N., Parikh, P., Bisht, B., . . . Paul, M. K. (2023). Lung cancer immunotherapy: progress, pitfalls, and promises. *Molecular cancer*, 22(1), 40.
- Li, Y., Wang, X., Li, S., Wang, L., Ding, N., She, Y., & Li, C. (2025). Therapeutic Effects of Natural Products in the Treatment of Chronic Diseases: The Role in Regulating KEAP1–NRF2 Pathway. *The American Journal of Chinese Medicine*, 53(01), 67-96.
- Madeddu, C., Donisi, C., Liscia, N., Lai, E., Scartozzi, M., & Maccio, A. (2022). EGFR-mutated non-small cell lung cancer and resistance to immunotherapy: role of the tumor microenvironment. *International Journal of Molecular Sciences*, 23(12), 6489.
- Mukherjee, A. G., & Gopalakrishnan, A. V. (2023). The mechanistic insights of the antioxidant Keap1-Nrf2 pathway in oncogenesis: a deadly scenario. *Medical Oncology*, 40(9), 248.
- Nadal, E., Palmero, R., & Muñoz-Pinedo, C. (2019). Mutations in the antioxidant KEAP1/NRF2 pathway define an aggressive subset of NSCLC resistant to conventional treatments. *Journal of Thoracic Oncology*, 14(11), 1881-1883.
- Padinharayil, H., Varghese, J., John, M. C., Rajanikant, G. K., Wilson, C. M., Al-Yozbaki, M., . . . Dey, A. (2023). Non-small cell lung carcinoma (NSCLC): Implications on molecular pathology and advances in early diagnostics and therapeutics. *Genes & Diseases*, 10(3), 960-989.
- Slama, M., Slougui, N., Benaissa, A., Nekkaa, A., Sellam, F., & Canabady-Rochelle, L. (2024). *Borago Officinalis* L.: A Review On Extraction, Phytochemical, and Pharmacological Activities. *Chemistry & Biodiversity*, 21(5), e202301822.
- Šutić, M., Vukić, A., Baranašić, J., Försti, A., Džubur, F., Samaržija, M., . . . Knežević, J. (2021). Diagnostic, predictive, and prognostic biomarkers in non-small cell lung cancer (NSCLC) management. *Journal of personalized medicine*, 11(11), 1102.
- Tan, Y., Zhu, Q., Yang, M., Yang, F., Zeng, Q., Jiang, Z., & Li, D. (2024). Tetrandrine activates STING/TBK1/IRF3 pathway to potentiate anti-PD-1 immunotherapy efficacy in non-small cell lung cancer. *Pharmacological Research*, 207, 107314.
- Wang, B., Zhang, F., Wu, X., & Ji, M. (2024). TBK1 is paradoxical in tumor development: a focus on the pathway mediating IFN-I expression. *Frontiers in immunology*, 15, 1433321.
- Wang, Q., Ren, Z., Zhao, J., Zheng, T., Tong, L., Liu, J., . . . Tang, S. (2024). Mechanism and Application Prospects of NLRC3 Regulating cGAS-STING Pathway in Lung Cancer Immunotherapy. *International Journal of Medical Sciences*, 21(13), 2613.
- Wei, C., Liu, M., & Zhang, W. (2025). Programmed cell death protein 1 in cancer cells. *Cell Communication and Signaling*, 23(1), 185.
- Willmore, Z. N., Coumbe, B. G., Crescioli, S., Reci, S., Gupta, A., Harris, R. J., . . . McCraw, A. (2021). Combined anti-PD-1 and anti-CTLA-4 checkpoint blockade: treatment of melanoma and immune mechanisms of action. *European Journal of Immunology*, 51(3), 544-556.
- Xu, K., Ma, J., Hall, S. R., Peng, R.-W., Yang, H., & Yao, F. (2023). Battles against aberrant KEAP1-NRF2 signaling in lung cancer: intertwined metabolic and immune networks. *Theranostics*, 13(2), 704.
- Yum, S., Li, M., Fang, Y., & Chen, Z. J. (2021). TBK1 recruitment to STING activates both IRF3 and NF- κ B that mediate immune defense against tumors and viral infections. *Proceedings of the National Academy of Sciences*, 118(14), e2100225118.
- Zhou, Y., Jiang, Z., Lu, H., Xu, Z., Tong, R., Shi, J., & Jia, G. (2019). Recent advances of natural polyphenols activators for Keap1-Nrf2 signaling pathway. *Chemistry & Biodiversity*, 16(11), e1900400.