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A Systematic Review of In Vitro Approaches for Evaluating Bioactive Natural Compound–Target Interactions in Early Drug Discovery

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Abstract: This study aims to systematically review and analyze in vitro approaches for evaluating bioactive natural compound–target interactions in early drug discovery, with myristicin highlighted as a representative example. Employing a qualitative descriptive research design, this study utilized a library-based method through the comprehensive analysis of scientific articles, books, and reports published between 2015 and 2025. Data collection involved literature screening and document analysis from peer-reviewed journals, while data analysis followed an inductive thematic approach encompassing identification, reduction, categorization, and synthesis of findings. The results indicate that integrating in vitro assays with computational (in silico) modeling significantly enhances predictive accuracy, efficiency, and mechanistic understanding in early drug discovery. Myristicin demonstrated multitarget bioactivity, including anti-inflammatory, antimicrobial, antioxidant, and anticancer effects, primarily through modulation of COX-2, PI3K/Akt/mTOR, and P-glycoprotein pathways. These findings reinforce the theoretical framework of polypharmacology, supporting the concept that natural compounds often act through multi-target interactions rather than single-receptor specificity. The study contributes to pharmacognosy and molecular pharmacology by providing a conceptual and methodological model for integrating experimental and computational drug discovery approaches. The implications extend to both academic and industrial domains, promoting standardized in vitro validation and translational research for natural product–based drug development.

Keywords: In Vitro Methods, Bioactive Natural Compounds, Myristicin, Drug Discovery, Molecular Interactions.

Introduction

Natural products have long been a cornerstone in early-stage drug discovery, serving as abundant sources of structurally diverse bioactive compounds with therapeutic potential (De Almada-Vilhena et al, 2024). The evolution of in vitro approaches has significantly accelerated the identification and validation of compound–target interactions, a critical step in modern pharmacological research (Li et al, 2021). With the increasing demand for more efficient and cost-effective drug development pipelines, in vitro systems have become indispensable for screening large libraries of natural compounds while reducing ethical and logistical constraints associated with in vivo studies (Chunarkar-Patil et al, 2024).

Recent advances in high-throughput in vitro assays have transformed natural product research by enabling rapid evaluation of biological activity and mechanistic elucidation before preclinical testing (De Almada-Vilhena et al, 2024). The pharmaceutical sector faces mounting pressure to discover safer and more targeted drugs, especially as the limitations of traditional synthetic drug discovery—such as low hit rates and safety concerns—become increasingly evident (Zhen et al, 2025). Consequently, leveraging in vitro models offers an efficient alternative to evaluate pharmacological efficacy, toxicity, and bioavailability at the molecular level (Mansouri et al, 2025).

In vitro methodologies, including enzyme assays, cell-based systems, and biochemical interaction models, provide critical insights into compound bioactivity and selectivity (Chunarkar-Patil et al, 2024). These approaches have been complemented by integrative techniques, such as in silico docking and AI-assisted modeling, that enhance predictive accuracy and reduce the number of compounds requiring experimental validation (Ugbaja et al, 2025). Such integration exemplifies the paradigm shift toward data-driven natural compound screening in early-stage drug development (Cava & Castiglioni, 2020).

Despite their clear advantages, in vitro models face challenges in replicating the complex physiological context of living systems. The translation of in vitro findings to in vivo relevance remains an ongoing concern (Zhen et al, 2025). Moreover, the biological complexity of natural compounds, characterized by multi-target interactions, demands innovative experimental frameworks that combine precision with scalability (Li et al, 2021).

The urgency of improving early drug discovery methodologies is further underscored by the rising global burden of chronic diseases such as cancer, neurodegenerative disorders, and autoimmune conditions (Mansouri et al, 2025). In this context, bioactive natural compounds—owing to their structural diversity and biological compatibility—offer unparalleled potential for identifying novel therapeutic agents (Xu et al, 2024). This has spurred interest in systematic in vitro evaluations to elucidate their mechanisms of action and optimize lead selection.

A particularly relevant example is myristicin, a naturally occurring phenylpropene found in nutmeg, parsley, and other aromatic plants. Studies have demonstrated that myristicin interacts with key enzymatic targets associated with neuroprotection, anti-inflammatory activity, and detoxification pathways (Li et al, 2021). Through in vitro enzyme inhibition and receptor-binding assays, myristicin's activity against cytochrome P450 enzymes and monoamine oxidases has been characterized, revealing its potential as a neuromodulatory and chemopreventive agent (De Almada-Vilhena et al, 2024).

However, despite promising preliminary findings, comprehensive mechanistic understanding of such interactions remains limited. This knowledge gap underscores the necessity of systematic in vitro evaluations, supported by standardized protocols and cross-platform validation (Zhen et al, 2025). Furthermore, the integration of molecular docking, multi-omics analyses, and machine learning models now offers a pathway to overcome traditional limitations in experimental reproducibility and biological interpretation (Periwal et al, 2022).

Modern drug discovery increasingly depends on this synergistic integration between computational and experimental methods (Ugbaja et al, 2025). Computational predictions refine target identification, while in vitro verification ensures biological relevance. This interplay not only reduces resource expenditure but also enhances the reliability of drug-target mapping (Cava & Castiglioni, 2020).

The trend toward artificial intelligence and automation in in vitro drug testing further strengthens the analytical power of these methods. AI-assisted screening platforms are now capable of simulating binding dynamics, predicting metabolic stability, and prioritizing compounds with favorable pharmacokinetic profiles (Xu et al, 2024). In combination with biochemical assays, such tools enable the rapid translation of natural product data into actionable pharmacological insights (Zhen et al, 2025).

Nevertheless, challenges persist regarding data standardization, cross-validation between laboratories, and the translation of in vitro potency into clinically relevant efficacy (Li et al, 2021). Addressing these limitations requires multi-disciplinary collaboration, involving biochemists, computational biologists, and pharmacologists (Mansouri et al, 2025).

The systematic review presented in this article synthesizes current advancements in in vitro methodologies for evaluating bioactive natural compound–target interactions, emphasizing both methodological strengths and research gaps. By doing so, it aims to provide a comprehensive framework for improving early drug discovery processes (De Almada-Vilhena et al, 2024).

This study also highlights how myristicin exemplifies the broader class of naturally derived molecules with pleiotropic activities that challenge conventional target-specific paradigms (Li et al, 2021). Understanding its multifaceted interactions can inform more rational approaches to drug development and toxicity prediction.

Ultimately, the urgency to refine in vitro systems stems from the growing recognition that drug discovery must balance innovation with translational feasibility (Zhen et al, 2025). Natural compounds, through rigorous in vitro and computational assessments, may serve as bridges between traditional medicine and modern pharmacology (Ugbaja et al, 2025).

Therefore, the main objective of this article is to systematically review the diversity of in vitro approaches employed in evaluating bioactive natural compound–target interactions, with a focus on optimizing their integration into early drug discovery pipelines. The expected outcomes include a clearer understanding of methodological trends, practical recommendations for laboratory standardization, and theoretical insights into the dynamic nature of compound–target relationships (Xu et al, 2024).

In theoretical terms, this review contributes to the conceptual foundation of pharmacognosy and molecular pharmacology by elucidating how in vitro data informs drug design. Practically, it offers guidance for developing efficient screening workflows that can shorten discovery timelines and enhance translational reliability (De Almada-Vilhena et al, 2024). Through these contributions, the article seeks to bridge the gap between empirical bioassay data and computational prediction, advancing the frontier of natural product–based drug discovery.

Methodology

This study employs a qualitative research design with a descriptive approach through library-based study (literature review). The qualitative method was selected for its ability to explore complex scientific phenomena and interpret data in a non-numerical, contextualized manner (Bingham, 2023) (Pratt, 2025). The descriptive approach was adopted to systematically present and interpret the existing body of knowledge related to in vitro methodologies for evaluating bioactive natural compound–target interactions in early drug discovery (Abraham & P, 2024) (Doyle, 2019). This design allows a comprehensive understanding of how current research trends, techniques, and innovations contribute to improving early drug screening processes using natural bioactive compounds.

The data sources used in this study include a wide range of academic and scientific materials—books, peer-reviewed journal articles, and official scientific reports—focusing on in vitro experimental approaches, bioassay validation, molecular docking, and computational modeling. The sources were primarily retrieved from established scientific databases such as Frontiers in Chemistry, Pharmaceuticals, Scientific Reports, Biomedicines, and Journal of Pharmaceutical Analysis, among others (De Almada-Vilhena et al, 2024) (Mansouri et al, 2025) (Ugbaja et al, 2025) (Xu et al, 2024) (Zhen et al, 2025). Supplementary literature on qualitative methodology and library research theory was also integrated to support the study's methodological framework (Bandaranayake, 2024) (Granikov et al, 2020) (Togia & Malliari, 2017).

Data collection techniques were conducted through an extensive literature search and document analysis. The process involved systematically identifying, screening, and selecting relevant academic sources that align with the research objectives. The study adopted a systematic review framework, including key stages such as topic refinement, literature search using defined keywords, inclusion/exclusion screening, and extraction of significant methodological and empirical findings (Cava & Castiglioni, 2020) (Chunarkar-Patil et al, 2024). Library research methods were employed to critically analyze both conceptual and empirical studies, ensuring that the reviewed materials provided substantial contributions to understanding in vitro experimental design and compound–target interaction analysis (Jimenez et al, 2024).

The data analysis procedure followed a qualitative thematic analysis model involving several key stages: (1) data identification and familiarization, (2) data reduction and coding, (3) categorization of conceptual themes, and (4) inductive interpretation and synthesis of findings (Belotto, 2018) (Bingham, 2023). The process adhered to an iterative cycle that continuously compared themes and patterns across studies, allowing emergent insights into methodological convergence and divergence. The coding process was both inductive and abductive, aligning new conceptual interpretations with existing theoretical frameworks (Fife & Gossner, 2024) (Vila-Henninger, 2022).

Inclusion criteria for the literature review encompassed peer-reviewed articles published between 2015 and 2025 that addressed in vitro evaluation of natural compound–target interactions, early drug discovery processes, or methodological advancements in biochemical and computational screening. Studies with non-experimental or anecdotal evidence were excluded. To ensure data validity and trustworthiness, the review employed

triangulation of sources—cross-referencing findings from different scientific journals, disciplines, and methodologies—to establish the credibility and consistency of interpretations (Bingham, 2023) (Kalpokaite & Radivojevic, 2018). In addition, the conceptual peer-review process was used to refine interpretations and enhance methodological rigor (Pratt, 2025).

Finally, this methodological framework ensures that the qualitative-descriptive approach through library-based research effectively captures the current scientific discourse on in vitro methodologies in early drug discovery. It also validates the integrative model that connects empirical laboratory findings with computational insights and theoretical perspectives on molecular interactions. The combination of rigorous data analysis and methodological transparency strengthens the study's reliability and ensures its findings are both relevant and reproducible within the broader scientific community (De Almada-Vilhena et al, 2024) (Li et al, 2021) (Zhen et al, 2025).

Result and Discussion

The systematic review of in vitro approaches for evaluating bioactive natural compound–target interactions in early drug discovery revealed three central findings: (1) methodological integration between in vitro and in silico systems significantly enhances target validation efficiency) ((2) in vitro assays remain the cornerstone for functional confirmation of computational predictions) (and (3) myristicin emerges as a key example of a multifunctional bioactive compound with diverse target interactions validated through both in vitro and in silico evidence.

1. Overview of In Vitro Approaches for Bioactive Compound Evaluation

The literature synthesis demonstrates that in vitro methods—such as enzymatic inhibition, cell-based assays, and pathway-targeted testing—play a crucial role in the early phases of natural compound screening. Techniques including cytotoxicity assays, antioxidant evaluations, and receptor-based molecular testing (e.g., estrogen receptor and PI3K/Akt/mTOR pathway analysis) are frequently applied to elucidate biological mechanisms (Bao & Muge, 2021) (Foudah et al, 2022) (Pang et al, 2018). The combination of in vitro and in silico analyses (molecular docking and ADME prediction) optimizes the accuracy of compound–target characterization while reducing experimental redundancy (Khairy et al, 2023) (Shtaiwi et al, 2024).

2. Integration of Network Pharmacology and Computational Modeling

Network pharmacology and molecular docking approaches have been extensively used to map multitarget interactions and predict pharmacological pathways of bioactive molecules (Pradeep et al, 2025) (Sakle et al, 2020). These computational tools enable visualization of multi-target networks, revealing potential synergistic effects and off-target implications. The integrated workflow—consisting of in silico prediction followed by in vitro validation—was consistently emphasized as the most effective method for identifying molecular mechanisms and guiding preclinical prioritization of drug candidates (De Sena Murteira Pinheiro et al, 2024) (Mansouri et al, 2025).

3. Case Study: Myristicin as a Model Bioactive Compound

A focused case study on myristicin, a major constituent of Petroselinum crispum essential oil, highlights its pharmacological versatility. In vitro and in silico findings reveal its strong binding affinities to multiple targets such as cyclooxygenase-2 (COX-2), N-myristoyl transferase, and cytochrome P450 14α-demethylase, confirming its potent anti-inflammatory and antimicrobial properties (Foudah et al, 2022). Furthermore, myristicin demonstrates promising anticancer activity by inhibiting hepatocellular carcinoma cell proliferation, migration, and invasion through suppression of the PI3K/Akt/mTOR signaling cascade (Bao & Muge, 2021).

4. Multidrug Resistance (MDR) Reversal and Oncological Implications

The compound also exhibits an ability to reverse multidrug resistance (MDR) in cancer cells by modulating P-glycoprotein activity, effectively enhancing chemotherapy sensitivity (Seneme et al, 2022). Such effects indicate that myristicin may serve as a chemosensitizing agent, particularly in drug-resistant cancers. Comparative studies with previous literature (Ansory et al, 2021) (Seneme et al, 2022)show that while the mechanisms of action overlap in targeting ATP-binding transporter proteins, myristicin demonstrates broader inhibitory coverage due to its polyfunctional aromatic structure.

5. Summary of In Vitro Findings

Table 1. In Vitro Approach and Myristicin Interaction

Approach	Molecular Target/Pathway	Key Findings	Source
Anti-inflammatory / Antimicrobial Assay	COX-2, N-myristoyl transferase	Strong binding affinity) (significant antioxidant activity	(Foudah et al, 2022)
Cytotoxicity on Cancer Cells	PI3K/Akt/mTOR	Inhibition of cell proliferation, migration, and invasion	(Bao & Muge, 2021)
MDR Reversal Assay	P-glycoprotein	Increased chemosensitivity) (reduced drug efflux	(Seneme et al, 2022)
Molecular Docking Validation	HSP90A, PTGS2, DHODH	Predicted inhibition of skin cancer-related targets	(Ansory et al, 2021)

This comparative synthesis underscores myristicin's multi-target mechanism and its potential for repurposing across multiple therapeutic domains.

6. Comparative Insights and Research Implications

Compared with earlier natural compound studies, myristicin demonstrates an unprecedented breadth of validated targets—ranging from inflammatory enzymes to kinases and efflux transporters—confirming its polypharmacological potential (Khairy et al, 2023) (Pradeep et al, 2025). Unlike conventional single-target approaches, in vitro and in silico validation of myristicin supports the paradigm of multitarget-directed ligands (MTDLs) in drug discovery (De Sena Murteira Pinheiro et al, 2024). The results collectively suggest that in vitro methodologies, when integrated with computational modeling, provide a robust framework for identifying, validating, and optimizing bioactive natural products in early-stage pharmacological research.

Discussion

The findings of this systematic review highlight the increasing sophistication of in vitro methodologies for studying bioactive natural compound–target interactions, particularly in the context of early drug discovery. The results indicate that integrating in vitro bioassays with computational approaches (in silico) enhances predictive accuracy, reduces screening redundancy, and provides mechanistic clarity regarding molecular interactions (Foudah et al, 2022) (Khairy et al, 2023) (Sakle et al, 2020). This hybrid approach bridges the traditional gap between biochemical testing and computational pharmacology, strengthening the translational potential of preclinical research (Pradeep et al, 2025).

From a theoretical standpoint, the integration of in vitro and in silico approaches supports the multi-target drug discovery paradigm, as described by De Sena Murteira Pinheiro et al. (2024) and Mansouri et al. (2025). This paradigm acknowledges that natural compounds rarely act through a single target but rather exert therapeutic efficacy through synergistic modulation of multiple pathways. For example, myristicin's ability to bind diverse targets such as COX-2, N-myristoyl transferase, and cytochrome P450 enzymes reflects a pleiotropic mechanism that aligns with network pharmacology models (Bao & Muge, 2021) (Foudah et al, 2022). These findings validate the theoretical concept of polypharmacology, where therapeutic benefit emerges from collective pathway regulation rather than isolated receptor antagonism.

In contextualizing these results within prior research, this review aligns with earlier discoveries that emphasized the role of natural compounds as modulators of inflammation, oxidative stress, and cancer progression (Pang et al, 2018) (Sakle et al, 2020). However, the novel contribution here lies in demonstrating that in vitro confirmation of in silico predictions can identify key molecular nodes, such as the PI3K/Akt/mTOR pathway and P-glycoprotein, which are critical in drug resistance and cell survival. Specifically, myristicin's suppression of PI3K/Akt/mTOR signaling in hepatic carcinoma (Bao & Muge, 2021) provides compelling evidence of its potential as a lead anticancer compound. Moreover, its inhibition of P-glycoprotein (Seneme et al, 2022) presents a promising avenue for overcoming multidrug resistance, a longstanding barrier in oncology.

The implications of these findings are significant. First, they suggest that in vitro platforms, when coupled with in silico modeling, can serve as robust preclinical predictors of bioactivity, reducing dependence on costly in vivo studies. Second, these results reinforce the importance of considering molecular promiscuity in drug discovery — not as a limitation but as a strategy for multi-target therapy design. Third, the validation of myristicin as a potential modulator of multiple cancer-related targets underscores the feasibility of repositioning dietary or phytochemical agents as therapeutic candidates (Ansory et al, 2021) (Foudah et al, 2022).

Nonetheless, several factors influence these outcomes. Experimental variability in extraction methods, assay conditions, and compound solubility may affect reproducibility across laboratories. For example, the bioactivity of volatile compounds like myristicin is sensitive to preparation techniques and solvent stability, potentially explaining minor inconsistencies between computational docking predictions and in vitro binding affinity results (Khairy et al, 2023). Additionally, while in vitro assays provide valuable mechanistic

insights, they fail to capture pharmacokinetic parameters such as absorption, distribution, and metabolic biotransformation that would be evident in in vivo systems (Shtaiwi et al, 2024).

Several limitations should also be acknowledged. Many studies rely heavily on molecular docking as the principal validation method, which, although informative, may not accurately represent biological complexity. Furthermore, the reviewed studies often used different cell lines, making direct cross-comparison difficult. Future research should address these gaps by employing standardized assay protocols and integrating multi-omics data (e.g., transcriptomics, proteomics) to contextualize in vitro responses with systemic biological effects (De Sena Murteira Pinheiro et al, 2024) (Mansouri et al, 2025). Additionally, extending the evaluation of myristicin to in vivo and clinical settings would confirm its pharmacodynamic potential and toxicity profile, solidifying its candidacy for therapeutic development.

Overall, this study advances the field of early drug discovery by illustrating how systematically integrated in vitro approaches can reveal the multi-dimensional pharmacology of bioactive natural compounds. The example of myristicin exemplifies how compound-target mapping, validated through both in vitro and computational analysis, contributes to identifying new therapeutic avenues for complex diseases such as cancer and neurodegeneration. By establishing methodological rigor and cross-validation between in vitro and in silico systems, this framework paves the way toward a more predictive and cost-efficient drug discovery process.

Conclusion

This qualitative synthesis concludes that the systematic integration of in vitro and in silico approaches provides a robust framework for understanding and validating the interactions between bioactive natural compounds and their molecular targets in early drug discovery. The findings highlight that such integration enhances screening efficiency and theoretical insight into the multitarget nature of natural compounds like myristicin, which exerts bioactivity through mechanisms such as COX-2 inhibition, PI3K/Akt/mTOR suppression, and P-glycoprotein modulation. These results strengthen the concept that therapeutic efficacy often arises from synergistic, multi-target interactions rather than single-target effects, enriching both pharmacognosy and network pharmacology. To advance this field, future research should emphasize translational studies, standardized in vitro validation, and comprehensive in silico analyses to improve predictive reliability before in vivo and clinical testing. Researchers are encouraged to apply triangulated methods integrating laboratory, computational, and theoretical approaches, while policymakers and pharmaceutical stakeholders should support standardized protocols and data-sharing systems to ensure reproducibility and resource efficiency. Expanding investigations to include multi-omics and broader natural compound libraries will further bridge the gap between experimental findings and clinical applications, strengthening the scientific and socio-cultural foundation for natural product–based drug discovery.

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