Open Journal of Biomedical Research
ISSN: 2966-6864
Published by DigitoPub | Digitodontics International Academy
DigitoPub
Open Access & Peer-reviewed
Indexed in: Crossref, ICI, MEDICUS, and ROAD

From Metabolomic Fingerprints to Therapeutic Leads: Integrating LC-MS/GC-MS, Network Pharmacology, Molecular Dynamics, and Artificial Intelligence in Natural-Product Drug Discovery

Rema A. Ballg[1] | Salah Neghmouche Nacer[2]*

[1]Department of Chemistry, Faculty of Sciences, University of Zawia, Al-Ajaylat, Libya.

[2]Laboratory of Applied Chemistry and Environment, Department of Chemistry, Faculty of Exact Sciences, University of El Oued, Algeria.

ABSTRACT

Natural products remain a major source of pharmacologically active scaffolds, but converting complex extracts into validated drug leads is still slow and uncertain. A major challenge is not metabolite detection itself, but establishing a reliable link between chemical identity, molecular target, mechanism of action, exposure, efficacy, and safety. LC–MS and GC–MS provide complementary metabolomic coverage, while spectral libraries, molecular networking, and dereplication strategies help prioritize compounds and avoid repeated isolation of known metabolites. Network pharmacology extends this analysis to compound–target–pathway relationships, whereas molecular docking and molecular dynamics (MD) provide structural hypotheses that can guide experimental testing. Artificial intelligence (AI) adds another layer of prioritization through spectral annotation, target and bioactivity prediction, ADMET assessment, and lead optimization. Yet greater computational complexity does not necessarily produce stronger biological evidence. Annotation errors, database bias, uncertain target assignments, inadequate molecular sampling, and poorly defined applicability domains can propagate across an integrated workflow and produce apparently coherent but weakly supported conclusions. This review examines how metabolomics, network pharmacology, molecular simulation, and AI can be combined without conflating prediction with validation. Particular emphasis is placed on confidence-ranked metabolite identification, reproducibility, data provenance, uncertainty, and the experimental evidence required to support mechanistic claims. We propose an evidence-gated workflow in which computational methods are used primarily to rank hypotheses and direct experiments, while biochemical validation, cellular target engagement, pharmacokinetics, in vivo efficacy, and toxicological assessment progressively establish biological confidence. Such integration can shorten the path from metabolomic fingerprints to therapeutic leads, provided that analytical confidence and experimental validation remain the basis for decision-making. (*Open J Biomed Res 2026;5:88-101*)

Keywords: Natural products, Metabolomics, Molecular docking, Artificial intelligence, Drug discovery.

ARTICLE INFO

*Corresponding author:

Salah Neghmouche Nacer

Email: neghmouchenacer-salah@univ-eloued.dz

Received: 17 July 2026

Accepted: 7 September 2026

Published: 10 September 2026

DOI:

https://doi.org/10.26629/ojbr.2026.12

Copyright: © 2026 by the authors.

Articles published in the *Open J Biomed Res* are licensed under a Creative Commons Attribution-Noncommercial 4.0 International License.

https://creativecommons.org/licenses/by-nc/4.0/

AUDIOABSTRACT

How to cite this article | Ballg RA, Neghmouche Nacer S. From Metabolomic Fingerprints to Therapeutic Leads: Integrating LC-MS/GC-MS, Network Pharmacology, Molecular Dynamics, and Artificial Intelligence in Natural-Product Drug Discovery. Open J Biomed Res 2026;5:88-101.

INTRODUCTION

Natural products (NPs) remain an important source of therapeutic agents and drug-like scaffolds. Biosynthetic pathways generate structurally diverse molecules with high stereochemical complexity and dense patterns of functional groups that are often underrepresented in conventional synthetic libraries. This chemical diversity has contributed substantially to anti-infective, anticancer, cardiovascular, and metabolic drug discovery. Increasingly, however, NPs are used not only as drugs themselves but also as starting points for semisynthetic optimization, pharmacophore identification, and pseudo-natural-product design. [1-4] Their structural richness comes with a practical cost. A crude extract may contain hundreds or thousands of detectable features spanning a wide concentration range, while stereochemical assignments and even molecular identities may remain uncertain. Moreover, an observed biological effect may reflect a single active constituent, several interacting compounds, assay interference, or nonspecific chemical reactivity. [2,3,5,6]

High-resolution mass spectrometry has greatly expanded the chemical information that can be extracted from such mixtures. LC–MS is well suited to polar, semi-polar, and thermolabile metabolites, whereas GC–MS provides highly reproducible analysis of volatile or derivatizable compounds. Tandem mass spectrometry, curated spectral libraries, feature-based molecular networking, and computational fragmentation have further increased the scale at which metabolites can be compared and annotated. [7-11] Greater analytical coverage, however, has not eliminated the identification problem. In many studies, thousands of features are detected but only a fraction can be assigned with sufficient confidence to support downstream biological interpretation. The principal challenge has therefore shifted from detecting signals to deciding which chemical assignments are reliable, which compounds are genuinely novel, and which candidates warrant biological investigation. [6,9-13]

Computational pharmacology has developed in parallel with these analytical advances. Network pharmacology can organize predicted compound–target–pathway relationships and is particularly attractive for chemically complex extracts. Molecular docking can suggest plausible ligand poses, while molecular dynamics (MD) examines how proposed complexes behave over time. End-point methods such as MM-PBSA and MM-GBSA may provide additional relative energetic ranking, and ADMET models can flag pharmacokinetic or toxicological liabilities before resource-intensive experiments are undertaken. Artificial intelligence (AI) and machine learning (ML) broaden this computational layer further by extracting patterns from molecular structures, mass spectra, bioactivity datasets, and multi-omics measurements. [14-20]

The value of combining these methods depends on how their outputs are interpreted. A predicted metabolite propagated into a target-prediction model, followed by docking, MD, and pathway analysis, may produce an internally consistent result even when the original structural assignment is wrong. Likewise, a stable MD trajectory does not establish target engagement, and a highly connected node in a pharmacological network does not demonstrate biological causality. Integration can therefore amplify information, but it can also propagate uncertainty. (Table 1) compares the distinct roles, strengths, and major failure modes of the principal technologies considered in this review.

Our focus is consequently not on assembling the largest possible computational

workflow, but on determining what level of evidence each method can reasonably provide. We examine an evidence-gated discovery strategy in which chemical identity is established with an explicit confidence level before compounds advance to biological prioritization; target predictions are treated as testable hypotheses; structural simulations are used to refine rather than prove those hypotheses; and pharmacological claims ultimately depend on orthogonal experimental evidence. Within this framework, LC–MS/GC–MS, network pharmacology, molecular simulation, ADMET prediction, and AI/ML occupy complementary but non-equivalent positions. (Fig. 1) summarizes the resulting workflow from natural-source selection and metabolomic profiling to experimental validation and lead optimization.

Scope and Novelty, existing reviews have provided valuable accounts of metabolomics-assisted natural-product discovery, network pharmacology, AI-enabled screening, and molecular modeling, but these areas are still frequently discussed as separate methodological domains. [12,21-24] Here, they are considered as successive decision layers in a single discovery process. The distinguishing principle is that the strength of a downstream claim cannot exceed the reliability of the evidence on which it is built. Thus, uncertain metabolite annotation limits the interpretation of target prediction; computational binding models require experimental target validation; and promising activity must ultimately be reconciled with exposure, pharmacokinetics, efficacy, and safety. This evidence hierarchy provides a practical framework for deciding not only which tools to use, but also when their outputs are sufficiently reliable to justify progression toward a therapeutic lead.

Table 1: Roles, strengths, and principal limitations of technologies used in integrated natural-product drug discovery.

Technology	Primary role	Major strength	Principal limitation
LC–MS/MS	Profiling nonvolatile and semi-polar metabolites	High sensitivity and broad chemical coverage	Ion/adduct complexity and annotation ambiguity
GC–MS	Profiling volatile or derivatizable metabolites	Reproducible EI spectra and retention indices	Restricted to volatile or derivatizable compounds
Molecular networking	Organization of MS/MS chemical families	Facilitates dereplication and analogue discovery	Spectral similarity alone does not establish molecular structure
Network pharmacology	Generation of compound–target–pathway hypotheses	Represents multi-component and multi-target relationships	Strongly influenced by database coverage and target-popularity bias
Molecular docking	Binding-pose generation and rapid ligand ranking	Efficient structural hypothesis generation	Docking scores should not be interpreted as experimental affinity or potency
Molecular dynamics	Analysis of conformational behavior and complex stability	Incorporates molecular flexibility, solvent, and time-dependent interactions	Conclusions depend on force field, simulation setup, and sampling
MM-PBSA/MM-GBSA	Approximate energetic refinement of simulated complexes	Computationally inexpensive relative ranking	Limited reliability for absolute binding free energies
AI/ML	Annotation, prediction, prioritization, and data integration	Scales to large and heterogeneous datasets	Vulnerable to data leakage, domain shift, bias, and limited interpretability

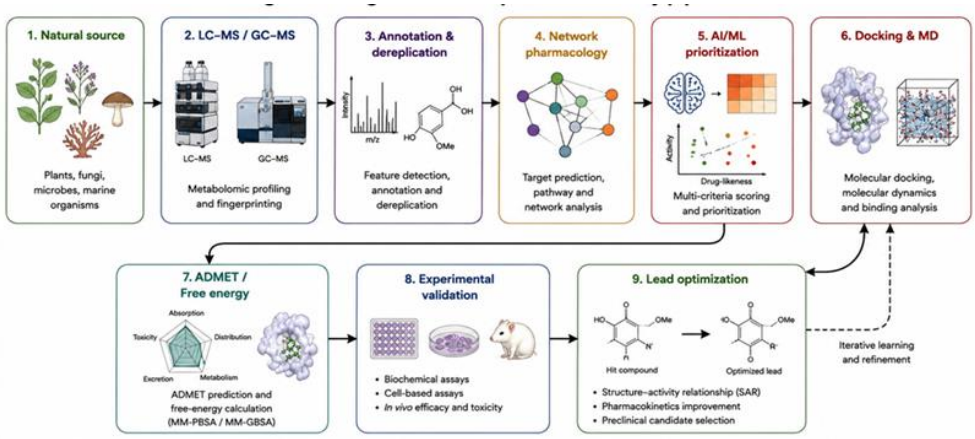


Fig. 1: Integrated natural-product discovery pipeline linking natural-source selection, LC–MS/GC–MS metabolomic profiling, annotation and dereplication, network pharmacology, AI/ML prioritization, docking and molecular dynamics, ADMET/free-energy assessment, experimental validation, and iterative lead optimization.

NATURAL PRODUCTS AS DRUG-DISCOVERY CHEMICAL SPACE

Natural products (NPs) occupy a distinctive region of chemical space, characterized by stereochemical complexity, high sp^3 content, and dense functionalization. These features can favor molecular recognition and provide scaffolds underrepresented in conventional libraries. [1-4] Yet structural complexity does not imply developability: poor solubility, permeability, metabolic stability, or synthetic accessibility can prevent an active metabolite from becoming a viable drug. NPs should therefore be valued not only as candidate drugs, but also as mechanistic probes, pharmacophores, and starting points for medicinal-chemistry optimization.

NP discovery also depends critically on provenance. Species identity, tissue, geography, developmental stage, collection conditions, extraction, storage, and analytical batch can alter the observed metabolome. Poorly controlled variation can propagate into network analyses and AI models, producing apparently robust associations that reflect experimental or biological confounders rather than pharmacology.

Evidence requirements should match the claim. Tentative MS/MS annotation may support dereplication and hypothesis generation, whereas a novel bioactive scaffold requires isolation and rigorous structural characterization, including NMR and stereochemical analysis. For known metabolites assigned a new mechanism, target engagement and functional validation become decisive. Thus, annotation confidence sets the reliability ceiling for downstream inference: computational sophistication cannot rescue an incorrect molecular identity.

LC-MS and GC-MS METABOLOMICS: COMPLEMENTARY WINDOWS ON CHEMICAL DIVERSITY

LC–MS and GC–MS interrogate complementary regions of natural-product chemical space. LC–HRMS is particularly suited to polar, semi-polar, thermolabile, and nonvolatile metabolites, whereas GC–MS remains highly effective for volatile constituents and derivatizable compounds. Platform selection should therefore be dictated by the chemistry and biological question rather than instrument availability.

In untargeted LC–MS, analytical confidence depends on chromatographic resolution, ionization mode, mass accuracy, MS/MS coverage, blanks, pooled quality-control samples, and batch control. Importantly, a feature is not necessarily a metabolite: isotopes, adducts, in-source fragments, and contaminants can inflate apparent chemical diversity. Feature grouping

and ion-identity approaches help reduce this redundancy. GC–MS offers an additional advantage through retention indices, which provide orthogonal evidence when combined with reproducible electron-ionization spectra.

A persistent weakness in NP studies is the use of *identified* for compounds supported only by accurate mass or tentative spectral matching. Exact mass rarely establishes structure, particularly for isomers. Annotation should instead be confidence-ranked, progressing from molecular formula or chemical class to probable structure and, ultimately, confirmation with authentic standards or complementary spectroscopic evidence (Fig. 2). Uncertain chemical identity should not become false precision simply because it enters a downstream computational workflow.

Molecular networking extends annotation beyond individual spectral matches by grouping related MS/MS spectra into chemical families. Feature-based molecular networking further integrates chromatographic abundance and sample or bioactivity metadata, enabling prioritization of metabolite families and analogues around known structures. [9-13] Its value, however, remains dependent on the quality of the underlying spectra: spectral similarity supports structural relationships, not structural proof.

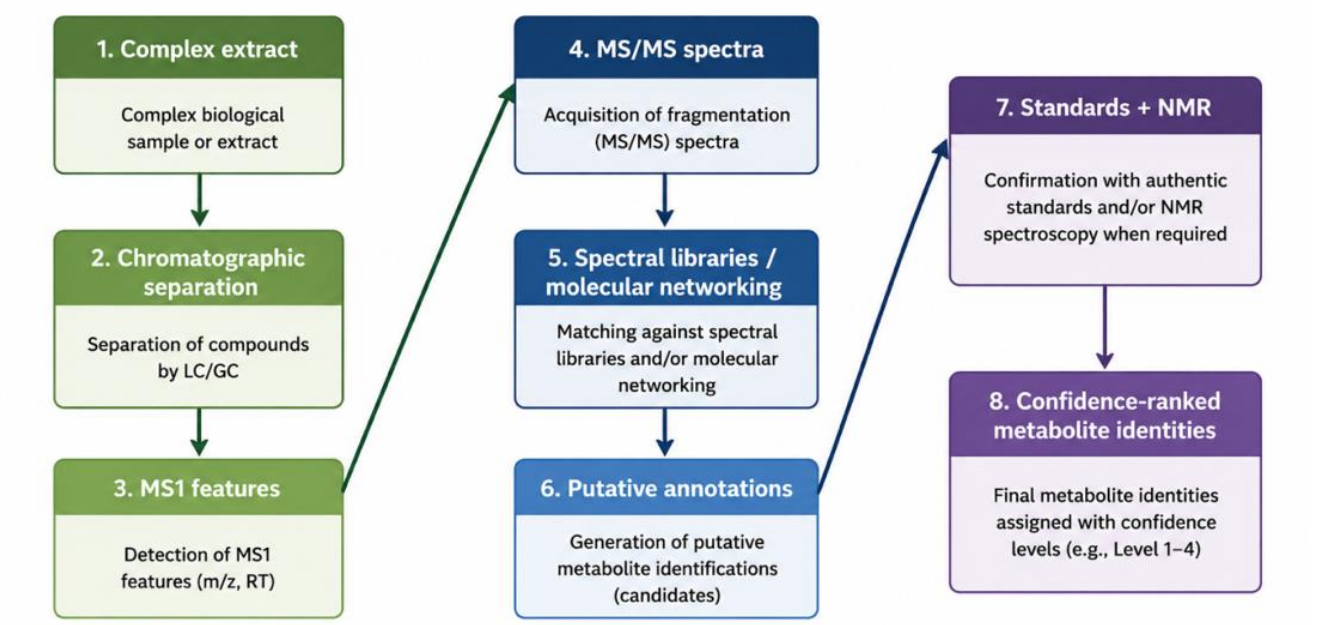


Fig. 2: Confidence-aware metabolite annotation. Structural assignments gain confidence through orthogonal evidence, progressing from MS-derived features and putative annotations to confirmation with authentic standards or complementary structural analysis.

DEREPLICATION, MOLECULAR NETWORKING AND METABOLITE PRIORITIZATION

Dereplication prevents resources from being spent rediscovering known chemistry. Reliable assignments should combine accurate mass, isotope patterns, MS/MS similarity, retention behavior, taxonomic context, and database evidence. [7,8] Database matches alone remain insufficient because spectral coverage is incomplete and deposited annotations may themselves be uncertain. Molecular networking adds chemical context by clustering related MS/MS spectra, allowing known metabolites to guide the recognition of unexplored analogues. Integration with bioactivity data can further prioritize active chemical families, but association is not

causation: co-elution, correlated biosynthesis, and mixture effects can falsely link a spectral feature to a phenotype. Prioritization should therefore integrate novelty, annotation confidence, abundance, bioactivity, target relevance, toxicity, and experimental tractability rather than rely on a single score. AI can strengthen this ranking, but only within a defined applicability domain. A precise prediction outside the model's chemical space is still an unreliable prediction.

NETWORK PHARMACOLOGY: FROM COMPOUND LISTS TO TESTABLE MECHANISMS

Network pharmacology is well suited to natural products because it models relationships among multiple compounds, targets, pathways, and disease processes. Typical workflows connect metabolite-associated targets with disease genes, protein–protein interaction networks, and pathway enrichment to generate mechanistic hypotheses for subsequent testing. [22,25] Its main limitation is database-driven circularity. Well-studied targets are overrepresented, disease-gene sets vary in quality, and target prediction often depends on similarity to known ligands. Consequently, highly connected hubs and recurrent pathways such as PI3K–AKT or MAPK may reflect database structure rather than causal biology. Network centrality is therefore a prioritization signal, not evidence of mechanism.

Metabolomics can strengthen network analysis by incorporating measured abundance rather than treating every reported constituent equally. Exposure filtering is equally important because compounds unlikely to reach a proposed target should not dominate mechanistic interpretation. For complex extracts, parent constituents should also be distinguished from host- or microbiome-derived metabolites that may represent the actual circulating species.

Docking and MD can refine network-derived hypotheses, but they do not constitute independent validation when they inherit the same compound and target assumptions. [26] Computational agreement strengthens a hypothesis only when the methods contribute genuinely independent evidence; biological mechanism ultimately requires experimental confirmation.

MOLECULAR DOCKING: USEFUL HYPOTHESIS GENERATOR, WEAK PROOF OF EFFICACY

Molecular docking provides plausible binding poses and approximate interaction scores, making it useful for prioritizing metabolites before experimental testing. [27-29] In natural-product discovery, its greatest value lies in comparing related compounds, identifying key binding interactions, and narrowing large candidate sets. Its predictive limits are substantial. Scoring functions simplify receptor flexibility, solvation, entropy, and protonation, while results depend strongly on protein preparation, binding-site definition, ligand state, cofactors, and structural waters. Redocking of co-crystallized ligands, pose inspection, and comparison with known active and inactive compounds should therefore be routine validation steps. [27-29] Most importantly, a better docking score does not imply greater potency or efficacy. Docking cannot establish affinity, selectivity, cellular activity, or agonist/antagonist behavior. Ensemble and induced-fit approaches can better represent receptor flexibility, but they do not convert docking into experimental evidence. [27-30] Docking should rank structural hypotheses, not prove pharmacological activity.

MOLECULAR DYNAMICS AND FREE-ENERGY REFINEMENT

Molecular dynamics (MD) extends docking by examining ligand–protein interactions over time in an explicit molecular environment. It can test pose stability, reveal water-mediated interactions, and identify conformational changes that static structures cannot capture. Common descriptors such as

RMSD, RMSF, hydrogen-bond occupancy, radius of gyration, and solvent-accessible surface area are informative, but none independently demonstrates binding. [31] MD reliability depends on force fields, ligand parametrization, protonation states, equilibration, simulation conditions, and sampling. A single 100-ns trajectory may describe local stability while missing slower transitions; replicate simulations can therefore be more informative than one apparently stable trajectory. Enhanced sampling may be required when relevant states are separated by substantial energy barriers. [31]

MM-PBSA and MM-GBSA provide inexpensive energetic refinement but are most defensible for relative ranking within chemically related series, not as absolute binding-affinity measurements. Their results remain sensitive to dielectric assumptions, entropy treatment, and trajectory selection. More rigorous alchemical approaches can improve relative free-energy estimates but require greater computational and methodological control. For natural-product studies, MD is most valuable as a stress test of a docking hypothesis. Pose instability, loss of critical interactions, or strong replicate dependence should lower confidence rather than be excluded from interpretation. A stable trajectory supports structural plausibility; it does not establish pharmacological activity.

ADMET AND DEVELOPABILITY: MOVING BEYOND BINDING

Binding alone does not define a therapeutic lead. Natural products may suffer from poor solubility, limited permeability, rapid metabolism, extensive conjugation, or toxicity, making early ADMET assessment essential for eliminating candidates whose exposure cannot support the proposed mechanism. *In silico* models can rapidly estimate physicochemical properties, permeability, CYP and transporter interactions, clearance, and toxicity. Their reliability, however, depends on the chemical space represented in the training data. Structurally unusual NPs may lie outside these applicability domains; predictions should therefore be interpreted with confidence estimates and verified experimentally through assays such as solubility, permeability, microsomal stability, and cytotoxicity. [32-35] The critical criterion is exposure–mechanism consistency. An interaction observed only at micromolar concentrations is unlikely to explain efficacy when free systemic exposure remains nanomolar, regardless of favorable docking or MD results. Conversely, high in vitro potency has limited value when rapid metabolism prevents target exposure. Developability should therefore be evaluated alongside mechanism, not appended after candidate selection.

ARTIFICIAL INTELLIGENCE ACROSS THE NATURAL-PRODUCT PIPELINE

Artificial intelligence (AI) is increasingly used across natural-product discovery for spectral annotation, bioactivity and target prediction, ADMET assessment, and molecular optimization. Graph neural networks and transformer-based models can learn complex chemical representations, while generative approaches can propose analogues optimized across multiple properties. [14-20] These applications are summarized in (Fig. 3).

The most credible role of AI is prioritization rather than proof. By integrating spectral, structural, bioactivity, docking, and omics information, AI can reduce large candidate spaces to compounds worth isolating or testing. Its value is particularly high when experimental material is limited. However, model complexity cannot compensate for uncertain chemical identity or poor-quality biological data. [5,15-19,21,24] AI performance is vulnerable to small datasets, class imbalance, assay inconsistency, missing negative data, and scaffold leakage. Random train–test splits can substantially overestimate performance when close analogues occur in both sets; scaffold-based, temporal, and external validation provide more realistic estimates of prospective utility. Applicability domains, uncertainty, and model

interpretability should therefore accompany predictions used to guide costly experiments. [5,15,21] Generative AI may extend natural-product scaffolds through semisynthetic or pseudo-natural-product design, but novelty alone is insufficient. Optimization must balance potency, selectivity, ADMET, and synthetic feasibility, followed by experimental validation. [14-20] AI should determine which hypotheses deserve testing—not which hypotheses are considered proven.

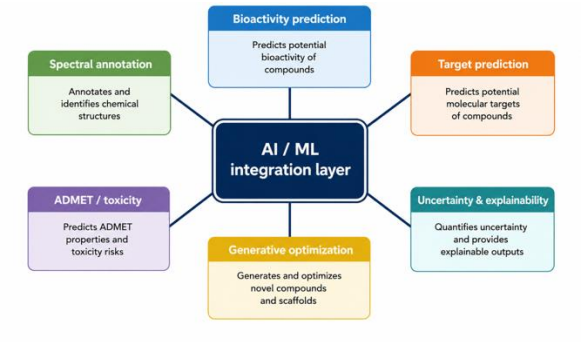


Fig. 3: AI/ML as a prioritization layer across natural-product discovery, supporting spectral annotation, bioactivity and target prediction, ADMET assessment, uncertainty evaluation, and molecular optimization.

AN INTEGRATED EVIDENCE-GATED WORKFLOW

An effective workflow should advance candidates according to evidence, not computational complexity. It begins with authenticated biological material, reproducible extraction, and quality-controlled LC–MS/GC–MS profiling, followed by feature processing, confidence-ranked annotation, dereplication, and molecular networking. Measured abundance and phenotypic data can then be integrated with network pharmacology to prioritize compounds and formulate testable target hypotheses. Practical progression criteria are summarized in (Table 2).

Docking evaluates structural plausibility, while MD and free-energy calculations refine selected hypotheses. Candidates that survive ADMET and exposure filtering should progress to biochemical or biophysical target validation, cellular target-engagement studies, and ultimately pharmacokinetic, efficacy, and safety assessment. Experimental results can then inform AI models and guide analogue optimization.

The defining feature of this workflow is its stopping rules. Weak structural annotation should not justify extensive simulation, and favorable docking should not justify in vivo studies without experimental target evidence. Each stage must either increase confidence or terminate progression. More computation cannot compensate for weak upstream evidence. (Fig. 4) summarizes this hierarchy from computational prediction to translational validation.

Table 2: Decision gates from metabolomic feature to therapeutic lead.

Gate	Key question	Go criterion	Stop/repair signal
1. Analytical	Is the feature real and reproducible?	QC-supported signal above blank/background	Artifact, contaminant, or unstable feature
2. Identity	Is structural confidence sufficient?	MS/MS, RI, authentic standard, or NMR appropriate to the claim	Ambiguous isomer or unsupported database match
3. Biological	Is activity associated with the candidate?	Dose–response relationship or orthogonal activity correlation	Assay interference or co-elution
4. Mechanistic	Is the target hypothesis plausible?	Network, structural, and biochemical coherence	Generic enrichment without target-specific support
5. Structural	Does the binding model withstand validation?	Validated docking and reproducible MD	Protocol failure or unstable pose
6. Developability	Can relevant exposure be achieved?	Acceptable solubility, permeability, stability, and safety	Exposure below the effective concentration
7. Experimental	Is target engagement demonstrated?	Biochemical/cellular engagement with functional effect	Phenotype without target linkage
8. Translational	Does efficacy occur at tolerated exposure?	PK/PD-linked in vivo efficacy	Effect only at unrealistic or intolerable exposure

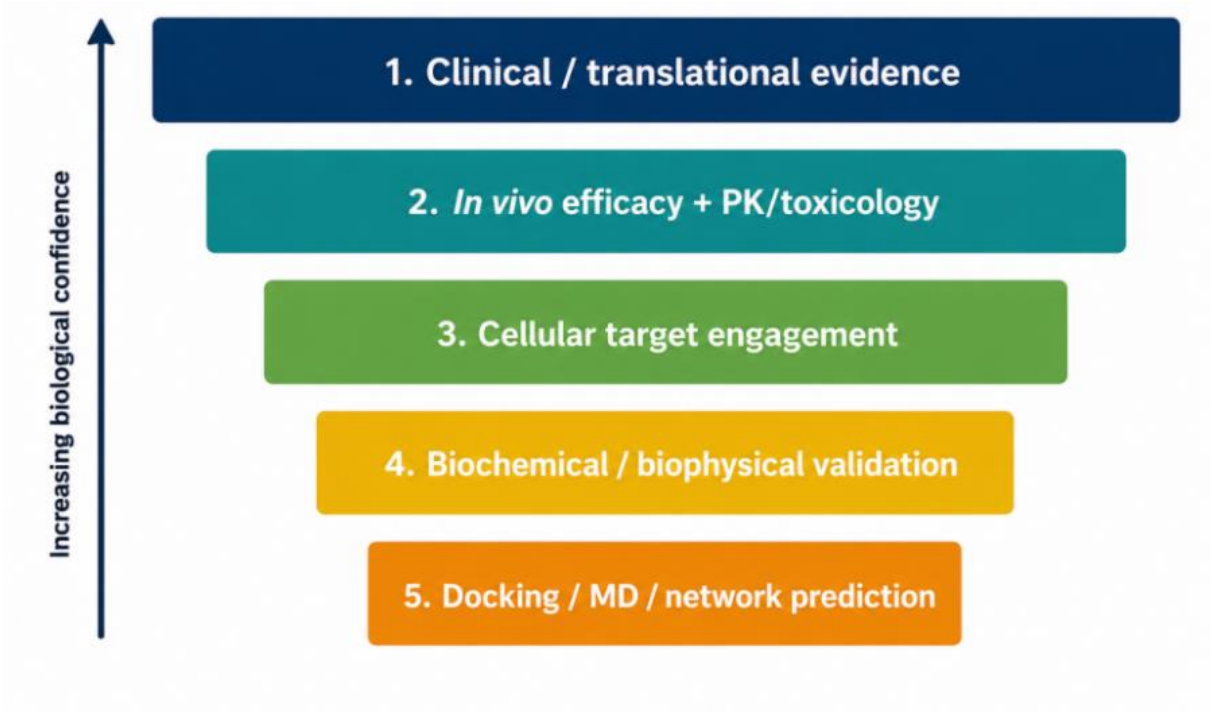


Fig. 4: Evidence ladder for natural-product lead claims. Computational predictions form the lowest level of evidence and gain biological credibility through biochemical validation, cellular target engagement, in vivo efficacy, pharmacokinetic and toxicological assessment, and ultimately translational evidence

DISEASE-FOCUSED APPLICATIONS AND REPRESENTATIVE INTEGRATED STUDIES

Integrated natural-product workflows are applicable across cancer, metabolic, neurodegenerative, inflammatory, and infectious diseases, but validation must reflect disease biology. Cancer studies require target engagement and selective activity in relevant tumor models; metabolic leads require exposure and physiological efficacy; CNS candidates require brain penetration and neurological safety; and anti-infective compounds require pathogen selectivity and resistance assessment.

Recent studies illustrate both the potential and limitations of integrated approaches. GC–MS profiling of *Cotula cinerea* essential oil combined docking, 300-ns MD, MM-PBSA, ADMET, and quantum-chemical analysis to prioritize cis-verbenyl acetate against colorectal-cancer-associated tankyrases. [36] *Artemisia campestris* phytochemicals were evaluated against AChE, BuChE, MAO-B, BACE-1, and GSK-3β as potential multi-target candidates for Alzheimer's disease, [37] while LC–MS profiling of *Ephedra alata* was linked to antioxidant and anticancer phenotypes. [38] These studies demonstrate efficient integration of analytical and computational evidence, but predicted targets still require direct experimental confirmation. Representative examples and their translational implications are summarized in (Table 3). The central lesson is simple: disease relevance cannot be inferred from computational convergence alone. The strongest integrated studies use computation to prioritize compounds and design decisive experiments, not to replace mechanistic validation.

Table 3: Representative integrated studies and their translational lessons.

Study/model	Analytical layer	Computational layer	Translational lesson
***Cotula cinerea* / colorectal cancer**	GC–MS essential-oil profiling	Multi-target docking, 300-ns MD, MM-PBSA, ADMET, and DFT	Strong prioritization pipeline; direct target validation remains essential
***Artemisia campestris* / Alzheimer's disease**	GC–MS phytochemical profiling	Multi-target docking, MD, ADMET, and quantum analysis	Supports multi-target prioritization in multifactorial disease
***Ephedra alata* / anticancer–antioxidant activity**	LC–MS metabolomic profiling	Pharmacophore/POM analysis	Connects measured chemistry with phenotype; target-level validation remains necessary
***Cucurbita maxima* / inflammation**	UPLC–ESI–MS/MS	COX-focused docking and ADMET	Integrates chemical profiling with in vitro/in vivo evidence
Natural products / type 2 diabetes	Literature/database-derived NP set	Network pharmacology, docking, and MD	Demonstrates staged computational prioritization in complex disease

REPRODUCIBILTY, REPORTING STANDRADS AND COMMON FAILURE MODES

Reproducibility is essential for integrated natural-product discovery. Raw analytical data, processing parameters, spectral libraries, compound identifiers, stereochemical assignments, target structures, docking protocols, software versions, force fields, MD inputs, and AI models or code should be reported or deposited whenever possible. Without these elements, complex workflows cannot be independently audited or reproduced. Minimum reporting requirements are summarized in (Table 4). [6,13,21,25,31]

Table 4: Minimum reporting requirements for metabolomics-to-lead studies.

Domain	Minimum information
Biological material	Taxonomic authentication, voucher/specimen, tissue, collection conditions, and storage metadata
Extraction	Solvent, ratio, time, temperature, replicates, and yield
LC/GC–MS	Instrument, column, gradient/program, ionization, mass range, blanks, QC, and acquisition mode
Annotation	Mass error, adduct, MS/MS evidence, retention data, library/database, and confidence level
Network pharmacology	Target and disease-gene sources, thresholds, database version/date, and enrichment correction
Docking	Protein structure, preparation, grid definition, protonation, ligand preparation, and redocking/validation
MD	Force field, ligand parameters, solvent, ions, equilibration, production time, and replicates
AI/ML	Dataset provenance, split strategy, class balance, metrics, external validation, uncertainty, and applicability domain
Experimental validation	Binding/function, cellular target engagement, PK/exposure, efficacy, and safety where justified

Failure modes occur at every stage. Metabolomics is weakened by inadequate quality control and overconfident annotation; network pharmacology by database bias and

generic enrichment; docking by unvalidated protocols and interpretation of scores as potency; MD by inadequate sampling and selective trajectories; and AI by data leakage, domain shift, and insufficient external validation. (Table 5) summarizes these recurring problems and more defensible alternatives. A simple principle should govern reporting: the strength of the claim must match the strength of the evidence. Rather than stating that a compound *binds* a target on computational evidence alone, authors should report that the interaction was *predicted* and requires experimental confirmation. Explicit uncertainty does not weaken a study; it defines what the evidence actually supports.

Table 5: Common overinterpretations and more defensible interpretations.

Weak claim	Why it is weak	Preferred interpretation
"LC–MS identified compound X" from exact mass alone	Isomers and isobars remain possible	Putatively annotated at a stated confidence level
"A better docking score means higher potency"	Scores are approximate and model-dependent	Prioritized binding hypothesis requiring experimental validation
"Stable RMSD proves binding"	RMSD measures structural deviation, not affinity	The pose remained stable under the specified simulation conditions
"A network hub is the main therapeutic target"	Hub degree is influenced by database structure and connectivity	Candidate node prioritized for perturbation or target-engagement studies
"AI accuracy is high" after a random split	Close analogues may leak between training and test sets	Report scaffold, temporal, or external validation and applicability domain
"Good ADMET profile" from one predictor	Models have endpoint-specific domains and uncertainties	Combine orthogonal predictions with targeted experimental ADME

FUTURE PERSPECTIVES

Natural-product discovery is moving toward closed-loop systems in which experiments continuously refine computational models. Automated fractionation, high-content phenotyping, rapid MS/MS annotation, and active learning could prioritize the next most informative experiment, while multi-omics and spatial metabolomics can connect chemical diversity with biological response and tissue localization. [23] Multimodal and foundation models may further integrate spectra, molecular structures, proteins, and biological data, potentially linking metabolite annotation directly to target, ADMET, and experimental prioritization. Their impact, however, will depend less on model size than on data quality, stereochemical accuracy, negative results, standardized metadata, and prospective validation. [15,21,39,40]

Advances in GPU computing, protein-structure prediction, and molecular simulation will also expand accessible chemical and target space. Hybrid AI–physics approaches are particularly promising, with AI generating hypotheses and physics-based methods testing structural plausibility. Predicted protein structures nevertheless require caution in flexible or ligand-induced binding sites. [31,39,40] The major challenge is therefore not adding more computational layers, but connecting them to decisive experiments. At the same time, accelerated discovery must preserve biological-resource provenance, sustainable sourcing, and equitable access and benefit sharing. The future of natural-product drug

discovery will depend on faster prediction, but even more on better evidence.

CONCLUSION

Natural-product drug discovery is shifting from isolated analytical and computational methods toward evidence-driven integration. LC–MS/GC–MS, molecular networking, network pharmacology, molecular simulation, ADMET prediction, and AI can collectively accelerate the transition from complex extracts to prioritized leads, but their value depends on the reliability of the evidence connecting each stage.

The critical requirement is evidence discipline: confidence-ranked chemical identification, explicit uncertainty, validated computational protocols, exposure-aware pharmacology, and orthogonal experimental confirmation. Computational agreement cannot substitute for biological proof, nor can sophisticated downstream modeling rescue uncertain upstream chemistry.

The most effective discovery pipelines will therefore use computation to prioritize what should be tested, not to declare what has been proven. By allowing experimental evidence to continuously refine chemical and computational hypotheses, this framework provides a rigorous path from metabolomic fingerprints to reproducible, mechanism-supported, and therapeutically credible leads.

AUTHOR CONTRIBUTIONS

Rema A. Ballg: Writing – original draft, literature review, investigation, data curation, and manuscript preparation. **Salah N. Nacer:** Conceptualization, methodology, supervision, validation, critical review, writing – review & editing, and final approval of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest concerning the research, authorship, and publication of this article.

FUNDING

This research received no external funding.

REFERENCES

1. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J Nat Prod. 2020; 83:770-803. doi:10.1021/acs.jnatprod.9b01285.
2. Atanasov AG, Zotchev SB, Dirsch VM; International Natural Product Sciences Taskforce, Supuran CT. Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov. 2021; 20:200-216. doi:10.1038/s41573-020-00114-z.
3. Rodrigues T, Reker D, Schneider P, Schneider G. Counting on natural products for drug design. Nat Chem. 2016; 8:531-541. doi:10.1038/nchem.2479
4. Grigalunas, M., Burhop, A., Zinken, S., Pahl, A., Gally, J. M., Wild, N., et al. Natural product fragment combination to performance-diverse pseudo-natural products. Nat Commun. 2021;12:1883. doi:10.1038/s41467-021-22174-4.
5. Saldívar-González FI, Aldas-Bulos VD, Medina-Franco JL, Plisson F. Natural product drug discovery in the artificial intelligence era. *Chem Sci*. 2021;13:1526-1546. doi:10.1039/d1sc04471k.
6. Gaudêncio SP, Bayram E, Lukić Bilela L, Cueto M, Díaz-Marrero AR, Haznedaroglu BZ, et al. Advanced Methods for Natural Products Discovery: Bioactivity Screening, Dereplication, Metabolomics Profiling, Genomic Sequencing, Databases and Informatic Tools, and Structure Elucidation. Mar Drugs. 2023; 21:308. doi:10.3390/md21050308.
7. Gaudêncio SP, Pereira F. Dereplication: racing to speed up the natural products discovery process. Nat Prod Rep. 2015;32:779-810. doi:10.1039/c4np00134f.
8. Pérez-Victoria I. Natural products dereplication: databases and analytical methods. Prog Chem Org Nat Prod. 2024;124:1–56. doi:10.1007/978-3-031-59567-7_1.
9. Aron AT, Gentry EC, McPhail KL, Nothias L F, Nothias-Esposito M, Bouslimani A, et al. Reproducible molecular networking of untargeted mass spectrometry data using GNPS. Nat Protoc. 2020;15:1954-1991. doi:10.1038/s41596-020-0317-5.
10. Nothias LF, Petras D, Schmid R, Dührkop K, Rainer J, Sarvepalli A, et al. Feature-based

molecular networking in the GNPS analysis environment. Nat Methods. 2020;17:905-908. doi:10.1038/s41592-020-0933-6.

11. Wang M, Carver JJ, Phelan VV, Sanchez LM, Garg N, Peng Y, et al. Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking. Nat Biotechnol. 2016;34:828-837. doi:10.1038/nbt.3597.
12. Deleray V, Dorrestein PC, Avalon NE. Molecules to medicine: advances in metabolomics for natural product drug discovery. Curr Opin Biotechnol. 2025;96:103373. doi:10.1016/j.copbio.2025.103373.
13. Wang Y, Wang Y, Zhang Z, Xu K, Fang Q, Wu X, et al. Molecular networking: an efficient tool for discovering and identifying natural products. J Pharm Biomed Anal. 2025;259:116741. doi:10.1016/j.jpba.2025.116741.
14. Stokes JM, Yang K, Swanson K, Jin W, Cubillos-Ruiz A, Donghia NM, et al. A deep learning approach to antibiotic discovery. Cell. 2020;180:688–702.e13. doi:10.1016/j.cell.2020.01.021.
15. Mullowney MW, Duncan KR, Elsayed SS, Garg N, van der Hooft JJJ, Martin NI, et al. Artificial intelligence for natural product drug discovery. Nat Rev Drug Discov. 2023;22:895–916. doi:10.1038/s41573-023-00774-7.
16. Muthuraj R, Chandrasekaran J. Nature meets machine: the AI renaissance in natural product drug discovery. Nat Prod Bioprospect. 2026;16:37. doi:10.1007/s13659-025-00589-6.
17. Othman ZK, Ahmed MM, Kasimieh O, Musa SS, Branda F, Cue EG, et al. Artificial intelligence for natural product drug discovery and development: current landscape, applications, and future directions. Intelligence-Based Medicine. 2025;12:100316. doi:10.1016/j.ibmed.2025.100316.
18. Xu T, Xu Y, Zhang J, Zhou Y, Feng H, Zhang A, et al. Advances in AI for predicting pharmacological properties of natural medicines. Life Sci. 2026;387:124180. doi:10.1016/j.lfs.2025.124180.
19. Wang B, Liu Q, Zhao W, Zhang T, Zhang D, Sutcharitchan C, et al. Revolutionizing drug discovery from natural products: the roles of artificial intelligence and multi-omics in accelerating innovation. Acta Pharm Sin B. 2026;16:4103–4127. doi:10.1016/j.apsb.2025.12.030.
20. Zhang C, Sun Q, Ablimit A, Dong H, Pan F, Wang H., et al. Molecular docking technology drives multidimensional applications of microbial natural products. J Mol Struct. 2025;1335:142044. doi:10.1016/j.molstruc.2025.142044.
21. Lee SS, Yoo YC. Data-quality-guided AI strategies for natural product drug discovery. Trends Pharmacol Sci. 2026;47:726–742. doi:10.1016/j.tips.2026.04.008.
22. Panossian A. Network pharmacology and natural products in modern drug discovery: emerging trends, challenges, and future directions. Pharmaceuticals (Basel). 2026;19:653. doi:10.3390/ph19050653.
23. Agbo CE, Nwankwo CK, Onyehalu JC, Agu MC, Opah C, Nworu CS. Computational pharmacology and in silico clinical trials for the development of drugs from natural products: a review of advances, opportunities, and challenges. J Pharmacol Exp Ther. 2026:104986. doi:10.1016/j.jpet.2026.104986.
24. Gangwal A, Ansari A, Siddique MUM, Sawale J, Padmane S, Wadekar R. Integrating artificial intelligence into drug discovery from medicinal plants: current applications and infrastructural challenges. Chem Biol Drug Des. 2026;108:e70372. doi:10.1111/cbdd.70372.
25. Panossian A. Trends and pitfalls in the progress of network pharmacology research on natural products. Pharmaceuticals (Basel). 2025;18:538. doi:10.3390/ph18040538.
26. Rahmani B, Akbari H, Esmaeili H, Solaimanian S, Mobasheri M, Shiri-Shahsavar MR. Discovering bioactive pharmaceuticals from natural products for type 2 diabetes mellitus using network pharmacology, molecular docking, and molecular dynamics. Sci Rep. 2025;15:43205. doi:10.1038/s41598-025-27173-9.
27. Aguiar C, Camps I. Molecular docking in drug discovery: techniques, applications, and advancements. Curr Med Chem. 2025;32:5924–5938. doi:10.2174/0109298673325827240926081845.
28. Pagadala NS, Syed K, Tuszynski J. Software for molecular docking: a review. Biophys Rev. 2017;9:91-102. doi:10.1007/s12551-016-0247-1
29. Pinzi L, Rastelli G. Molecular Docking: Shifting Paradigms in Drug Discovery. Int J Mol Sci. 2019;20:4331. doi:10.3390/ijms20184331
30. Amaro RE, Baudry J, Chodera J, Demir Ö, McCammon JA, Miao Y, et al. Ensemble docking in drug discovery. Biophys J. 2018;114:2271–2278.

doi:10.1016/j.bpj.2018.02.038.

31. Ahmed M, Maldonado AM, Durrant JD. From byte to bench to bedside: molecular dynamics simulations and drug discovery. BMC Biol. 2023;21:299. doi:10.1186/s12915-023-01791-z.

32. Ancuceanu R, Lascu BE, Drăgănescu D, Dinu M. In silico ADME methods used in the evaluation of natural products. Pharmaceutics. 2025;17:1002. doi:10.3390/pharmaceutics17081002.

33. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7:42717. doi:10.1038/srep42717.

34. Pires DEV, Blundell TL, Ascher DB. pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem. 2015;58:4066–4072. doi:10.1021/acs.jmedchem.5b00104.

35. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2018;46:W257–W263. doi:10.1093/nar/gky318.

36. Bouchagra S, Lanez E, Benamor ML, Bekkar Y, Neghmouche Nacer S, Bourougaa L, et al. GC/MS analysis and computational evaluation of C. cinerea EO constituents for colorectal cancer: molecular docking, dynamics, and quantum chemical insights into cis-verbenyl acetate. Comput Biol Chem. 2026;120:108754. doi:10.1016/j.compbiolchem.2025.108754.

37. Zouaghi N, Lanez E, Benamor ML, Neghmouche Nacer S, Lanez T, Bekkar Y, et al. Targeting Alzheimer's disease via phytochemicals from Artemisia campestris L.: GC/MS analysis with an integrated computational approach. Food Biosci. 2026;75:108128. doi:10.1016/j.fbio.2025.108128.

38. Elsharkawy ER, Neghmouche Nacer S, Ben Hadda T, Almalki FA. LC–MS-based metabolomic characterization and POM pharmacophore analysis of the bioactive methanolic extract of Ephedra alata. Sci Rep. 2026;16:11715. doi:10.1038/s41598-026-47537-z.

39. Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, et al. Highly accurate protein structure prediction with AlphaFold. Nature. 2021;596:583–589. doi:10.1038/s41586-021-03819-2.

40. Abramson J, Adler J, Dunger J, Evans R, Green T, Pritzel A, et al. Accurate structure prediction of biomolecular interactions with AlphaFold 3. Nature. 2024;630:493–500. doi:10.1038/s41586-024-07487-w.