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Editorial

Natural Compounds in Modern Medicinal Chemistry: Bridging Molecular Discovery, Biological Activity, and Therapeutic Applications

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1. Introduction

Natural compounds have always occupied a special place in medicinal chemistry. Long before the development of modern drug discovery platforms, naturally occurring substances provided the foundations for numerous therapeutic interventions. Even today, when synthetic chemistry and computational drug design offer access to enormous molecular libraries, natural products remain an important source of biologically relevant structures and pharmacological inspiration [1].

Their contribution to modern therapeutics is well established. Newman and Cragg demonstrated the continuing importance of natural products and their derivatives among approved drugs, particularly in oncology and infectious diseases. More recently, Atanasov and colleagues highlighted how advances in analytical technologies, genome mining, and molecular characterization have renewed interest in natural-product-based drug discovery [2].

What makes natural compounds particularly interesting is not simply their chemical diversity, but the biological context in which this diversity has evolved. Natural metabolites often possess complex molecular architectures, distinctive stereochemical arrangements, and multiple functional groups that interact with biological systems. These characteristics offer valuable opportunities for medicinal chemistry, although they also introduce challenges related to synthesis, characterization, stability, and pharmacological optimization [3].

The Special Issue *"Research Progress and Application of Natural Compounds—2nd Edition"* was developed against this background, with the aim of encouraging research into biologically active natural substances, their chemical properties, and their potential applications. Particular attention was paid to secondary metabolites, including flavonoids, phenazines, polyketides, peptides, and glycosides, as well as to approaches that combine natural compounds with nanostructured materials and other molecular systems.

As Guest Editors, we consider this area especially relevant because natural-product research is undergoing an important transition. The identification of a compound with biological activity, although scientifically valuable, is no longer sufficient to establish its therapeutic potential. Increasingly, the central questions concern how a compound works, whether its effects are reproducible, how its molecular properties can be improved, and whether experimental findings can ultimately support practical applications [4].

These questions provide a useful perspective for considering both the contributions of the present Special Issue and the directions future investigations should pursue.

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2. Natural Compounds as Starting Points for Molecular Innovation

One of the enduring strengths of natural products is their ability to introduce chemical structures that differ from those commonly represented in conventional synthetic libraries. Their complex ring systems, stereogenic centers, and three-dimensional architectures may create opportunities for molecular recognition that would otherwise remain unexplored. However, a naturally occurring structure should not necessarily be regarded as an optimized therapeutic molecule. Evolutionary selection favors biological functions within the producing organism, not the pharmacokinetic or safety requirements of human medicine. This distinction explains why structural modification remains so important. Natural compounds can serve as scaffolds for the synthesis of derivatives with improved potency, selectivity, solubility, or metabolic stability. In some cases, relatively small structural changes can substantially alter biological activity. In others, modification of a single functional group may reduce toxicity or improve interactions with a particular molecular target [5].

The challenge for medicinal chemists is to determine which structural features are essential for activity and which can be modified without compromising the desired biological effect. Structure–activity relationship studies remain central to this process, but their interpretation increasingly benefits from complementary computational approaches. Molecular docking, conformational analysis, and molecular dynamics can provide useful hypotheses concerning ligand–target interactions. Nevertheless, these methods are most informative when their predictions are examined alongside experimental observations. Particular attention should also be given to stereochemistry. Different stereoisomers may display markedly different biological properties despite sharing the same molecular formula and connectivity. A more detailed understanding of molecular geometry and conformational behavior may therefore help explain why certain natural scaffolds exhibit selectivity toward specific biological targets. In our view, future progress will depend on treating natural compounds not merely as substances to be screened, but as molecular platforms that can be investigated, modified, and developed through rational chemical strategies [6].

3. Understanding Biological Activity: Beyond Preliminary Screening

Natural products have been investigated for a wide range of biological effects, including antimicrobial, antioxidant, anti-inflammatory, and anticancer activities. These observations continue to generate valuable research questions and may identify compounds worthy of further investigation. However, the interpretation of biological activity is not always straightforward. For example, a compound that produces a strong antioxidant response in a chemical assay may not exert the same effect in a cellular environment. Similarly, the inhibition of cell proliferation does not necessarily demonstrate selective anticancer activity, particularly when comparable effects occur in nonmalignant cells. These distinctions are important because preliminary screening results are sometimes interpreted more broadly than the available evidence permits [7].

A major challenge is therefore to establish a clearer relationship between the observed biological response and the molecular events responsible for it. Natural compounds may interact with several biological targets simultaneously. Such multitarget activity can be relevant in complex diseases involving interconnected signaling pathways, but it may also complicate the identification of a primary mechanism of action. Future investigations should increasingly combine concentration–response experiments, target-engagement studies, pathway analysis, and functional biological measurements. The selection of experimental models is equally important. Biological activity observed under simplified laboratory conditions may change substantially in the presence of metabolic processes, tissue-specific interactions, or inflammatory and oxidative environments. For this reason, the transition from biochemical assays to cellular systems, more complex tissue models, and appropriately

designed in vivo investigations should be considered an essential part of the validation process. The objective should not simply be to demonstrate that a natural compound produces an effect, but to determine whether that effect is sufficiently specific, reproducible, and biologically meaningful to justify further development [8].

4. Addressing the Gap Between Molecular Potential and Practical Application

Despite substantial progress in natural-product research, translating promising experimental findings into therapeutic applications remains difficult. Several limitations recur throughout the field. Poor aqueous solubility can restrict absorption and complicate formulation development. Chemical instability may affect storage, administration, or biological exposure. Extensive metabolism can reduce the amount of active compound reaching its intended target, while insufficient selectivity may limit the therapeutic window. These challenges are not unique to natural products, but the structural complexity of many naturally occurring molecules can make them particularly difficult to address. Advanced drug delivery systems offer potential solutions. Lipid-based formulations, polymeric nanoparticles, cyclodextrin inclusion complexes, and other supramolecular platforms may improve solubility, stability, or controlled release. Such approaches are especially relevant to the scope of this Special Issue, which includes the development of nanostructured systems associated with natural compounds. Nevertheless, formulation improvement should be evaluated critically. Greater solubility or higher encapsulation efficiency does not automatically translate into improved therapeutic efficacy. The biological advantages of a formulation must be demonstrated through appropriate comparisons, including pharmacokinetic evaluation, toxicity assessment, and relevant functional outcomes. An equally important challenge concerns reproducibility.

The chemical composition of natural extracts may vary according to geographical origin, environmental conditions, harvesting procedures, extraction methods, and storage. Without adequate analytical characterization, these variations can complicate the comparison of experimental results. Future studies should therefore place greater emphasis on chemical standardization, transparent methodological reporting, and the use of well-characterized reference compounds. Such measures may appear primarily technical, but they are fundamental to the credibility and practical usefulness of natural-product research [9].

5. The Contribution of the Special Issue: Connecting Discovery with Application

The scientific value of a Special Issue should not be measured only by the number of articles it brings together. A thematic collection is also an opportunity to examine how individual investigations contribute to a broader research problem. For natural compounds, that problem is particularly clear: how can molecular diversity and experimental biological activity be translated into reliable scientific knowledge and, ultimately, useful applications? The present Special Issue was conceived to encourage contributions across the chemical and biological dimensions of natural-product research. Its scope encompasses several areas in which closer integration is needed: the identification and characterization of bioactive compounds, the investigation of their biological properties, the modification of molecular structures, and the development of technologies to improve their practical utility. These directions are interconnected. Chemical characterization establishes what is being investigated; biological studies determine what the compound does; mechanistic experiments help explain how it acts; and pharmaceutical or technological approaches explore how

its properties might be adapted for practical use. An important lesson emerging from contemporary natural-product research is that progress in one area cannot fully compensate for limitations in another. Detailed molecular characterization is of limited translational value without relevant biological evidence, just as promising pharmacological activity is difficult to establish when chemical identity, stability, or exposure remain uncertain [10]. The Special Issue provides a context in which these complementary approaches can be considered together. This integrated perspective is particularly important because it encourages a shift away from isolated observations toward research strategies that connect chemical properties to biological mechanisms and practical outcomes.

Key Findings and Scientific Contributions of the Special Issue

The articles published in the Special Issue "Research Progress and Application of Natural Compounds—2nd Edition" provide complementary perspectives on the discovery, molecular characterization, biological evaluation, and practical application of natural compounds. The seven contributions considered here encompass computational investigations of plant-derived metabolites, the pharmacological potential of cyclic peptides, experimental toxicology, anticancer drug development, pharmaceutical formulation, and environmentally relevant applications. Collectively, these studies demonstrate that the scientific value of natural compounds extends beyond their intrinsic biological activity and increasingly depends on the integration of chemical characterization, mechanistic investigation, and application-oriented experimental validation.

An important contribution to the computational characterization of natural compounds was made by Rêgo et al. [11], who investigated 954 phenolic compounds, including 715 flavonoids and 239 phenolic acids, by integrating the PhytoHub, Phenol-Explorer, ChEMBL, and FoodDB databases. The study combined molecular descriptors, drug-likeness metrics, protein interaction data, and dietary source information to establish a comprehensive framework for evaluating these compounds. Isoflavones exhibited the most favorable drug-likeness characteristics, with a mean Quantitative Estimate of Drug-likeness (QED) score of 0.62 ± 0.18. Furthermore, flavonoids demonstrated higher mean ChEMBL activity scores than phenolic acids (7.26 ± 1.09 versus 6.98 ± 0.94; $p = 0.014$), together with a broader range of documented protein targets. The moderate correlation between QED and DataWarrior scores ($r = 0.41$) also highlighted the complementary nature of different computational assessment methods. These findings illustrate how cross-database integration can support the prioritization of natural compounds for further pharmacological investigation, while emphasizing that computational drug-likeness and reported molecular interactions do not, on their own, establish therapeutic efficacy.

The therapeutic potential of structurally modified natural compounds was explored by Milan et al. [12], who investigated fatty acid esters of betulinic acid and their liposomal formulations against breast, colorectal, and lung cancer cell lines. Among the investigated formulations, liposomal butyryl-betulinic acid (But-BA-Lip) demonstrated particularly promising cytotoxic activity, with reported IC_{50} values of 30.57 μM in HT-29 colorectal cancer cells and 30.74 μM in NCI-H460 lung cancer cells after 48 h. These values were lower than those obtained for the reference compound 5-fluorouracil under the same experimental conditions. Additional analyses revealed morphological characteristics consistent with apoptosis and increased caspase-3/-7 activity, while the hen's egg test–chorioallantoic membrane (HET-CAM) assay indicated no detectable irritant effects under the tested conditions. This study demonstrates the potential advantages of combining chemical derivatization with liposomal delivery systems to modify the biological performance of naturally derived triterpenes. Nevertheless, the observed improvements remain preclinical and require further investigation of pharmacokinetics, tumor selectivity, and in vivo therapeutic efficacy.

The development of multifunctional pharmaceutical formulations was addressed by Creteanu et al. [13], who investigated lignin as a bioactive additive in chlorzoxazone-loaded matrix tablets. Three formulations containing 55, 60, and 65 mg of lignin were evaluated through physicochemical characterization, dissolution studies, and biological assays. The in vitro release profiles revealed an initial rapid-release phase during the first two hours, followed by a more prolonged release phase extending up to 36 h. Importantly, lignin incorporation also contributed to antioxidant and antimicrobial properties, with the formulation containing the highest lignin content (FLc) exhibiting the most pronounced biological activity among the tested formulations. These findings indicate that naturally derived polymers may serve functions beyond those traditionally associated with pharmaceutical excipients, potentially combining drug-release modulation with additional biological properties. The study therefore provides an example of how natural compounds can be integrated into pharmaceutical technologies to improve formulation functionality.

Natural peptides represent another important research direction highlighted in this Special Issue. Yang et al. [14] presented a comprehensive review of the chemical properties, preparation methods, and pharmacological effects of cyclic peptides isolated from Pseudostellaria heterophylla. The review identified 19 structurally characterized cyclic peptides, comprising nine heterophyllin-type and ten pseudostellarin-type compounds. Particular attention was given to heterophyllin B and its reported anticancer, anti-inflammatory, immunomodulatory, and other biological activities. The reviewed experimental evidence included modulation of signaling pathways associated with cellular proliferation, oxidative stress, and inflammation, including PI3K/AKT and AMPK-related mechanisms. The authors also discussed extraction, chemical synthesis, and biosynthetic production strategies, emphasizing the importance of obtaining these compounds through reproducible and scalable methods. This contribution highlights the relationship among peptide structural organization, biological activity, and the practical challenges of developing naturally occurring peptides as potential therapeutic agents.

Beyond pharmaceutical applications, the Special Issue also addressed the development of biologically active compounds for sustainable agricultural practices. Calderón-Urrea et al. [15] investigated the nematicidal properties of CED4-derived peptides and structurally modified CED4-like analogs. Peptides 2, 3, and 12 demonstrated particularly strong nematicidal activity, with complete mortality reported under specified experimental conditions in Caenorhabditis elegans and Meloidogyne incognita. The investigation also examined peptide combinations and their effects on nematode survival. Importantly, experiments involving CED-3 and CED-4 mutant strains provided evidence supporting the involvement of the endogenous programmed cell death pathway, particularly CED-3-dependent signaling, in peptide-induced mortality. These findings illustrate how knowledge of conserved biological pathways can guide the rational development of bioactive peptide sequences and potentially contribute to alternative pest-control strategies.

A complementary investigation by Calderón-Urrea et al. [16] examined the nematicidal activity of chalcone derivatives, with particular emphasis on synergistic interactions and potential effects on nontarget biological systems. Binary and ternary combinations of chalcones 17, 25, and 30 produced mortality rates reaching 90–100% in C. elegans within three days, with substantial activity also observed against M. incognita. The investigation incorporated soil microbiome analyses using 16S rRNA sequencing and cytotoxicity assessments in human pluripotent stem cells. Although some differences in microbial diversity measures were observed, the overall analysis of community composition did not identify significant treatment-related differences (PERMANOVA, $p = 0.648$). Moreover, the tested chalcones were generally well tolerated by human pluripotent stem cells at concentrations up to 1 μM. These findings suggest that combinations of natural-product-inspired molecules may offer

advantages in biological potency, while demonstrating the importance of simultaneously investigating environmental compatibility and potential toxicity in nontarget systems.

The importance of experimental toxicology was further emphasized by Sciandrone et al. [17], who investigated the arylnaphthalene lignan justicidin B using C. elegans as an in vivo model. The study demonstrated that treatment with 100 μg/mL did not significantly affect nematode vitality, fertility, or development under the investigated conditions. In contrast, repeated short-term exposure to 200 μg/mL produced a reduction in survival, associated with increased compound accumulation and the detection of potential metabolic derivatives. Interestingly, administration every two days did not produce significant changes in lifespan at the tested concentrations, suggesting that exposure frequency and compound accumulation may influence the observed toxicological response. These results demonstrate the usefulness of integrating organism-level functional endpoints with analytical measurements of compound distribution and metabolism. They also illustrate the contribution of alternative experimental models to preliminary safety assessment before investigations in more complex biological systems.

Taken together, the contributions of this Special Issue reveal several convergent scientific directions. First, the characterization of natural compounds increasingly benefits from integrated computational, analytical, and experimental approaches. Second, structural modification and advanced formulation strategies can substantially influence biological activity and pharmaceutical performance. Third, mechanistic investigations and appropriate toxicological assessments remain essential for interpreting promising experimental findings. Finally, the applications of natural compounds extend beyond conventional therapeutic development to include pharmaceutical excipients and environmentally relevant biological control strategies. Although the studies differ in their objectives and experimental systems, they collectively support a transition toward more integrated and application-oriented natural-product research. The next challenge will be to translate these findings into reproducible, mechanistically supported, and practically feasible applications through continued interdisciplinary investigation.

6. Future Perspectives: Where Should Natural-Product Research Go Next?

The next stage of natural-product research will likely be shaped by the convergence of experimental chemistry, computational methods, molecular biology, and pharmaceutical technology. Several developments are especially promising, although their value will depend on how effectively they address the limitations of current research.

6.1. Artificial Intelligence as a Tool for Better Scientific Decisions

Artificial intelligence is already influencing how researchers explore chemical space, predict molecular properties, and prioritize compounds for experimental investigation. Mullowney and colleagues described the potential of combining computational omics with machine-learning approaches to accelerate natural-product discovery. These methods may help identify previously overlooked biosynthetic pathways, predict biological activities, and guide the selection of molecular structures for further investigation. However, the usefulness of artificial intelligence depends on the quality of the information used to develop predictive models. Natural-product datasets frequently combine results obtained under different experimental conditions, sometimes with incomplete structural characterization or inconsistent biological endpoints. Such heterogeneity can limit model reliability. A central priority should therefore be the development of curated datasets containing experimentally verified chemical structures, standardized biological measurements, and clearly documented experimental conditions. Equally important is the distinction between computational prediction and experimental evidence. A predicted molecular interaction

may be useful for prioritizing experiments, but it should not be presented as proof of a biological mechanism. Artificial intelligence may be most valuable when it helps researchers formulate better hypotheses and allocate experimental resources more effectively [18].

6.2. Integrating Multi-Omics with Mechanistic Pharmacology

Many natural compounds influence multiple cellular processes, making their biological effects difficult to understand through isolated measurements. The integration of metabolomics, transcriptomics, proteomics, and other molecular profiling techniques may provide a more comprehensive picture of cellular responses. For example, metabolomic changes may reveal alterations in biochemical pathways that are not immediately apparent from conventional assays. Proteomic investigations may identify signaling networks affected by compound exposure, while transcriptomic data can provide information about broader cellular adaptation. However, these approaches also generate large quantities of data whose biological interpretation requires careful validation. The identification of an altered pathway does not necessarily establish a direct molecular target or demonstrate that the pathway is responsible for the observed phenotype. Future studies should therefore combine broad molecular profiling with targeted experiments designed to test causal relationships. This approach may be particularly useful for compounds acting on complex inflammatory, metabolic, or proliferative processes [19].

6.3. Designing Better Natural-Product Derivatives

Chemical optimization will remain an essential component of natural-product research. Rather than investigating large numbers of unrelated compounds, future studies may benefit from more focused strategies built around well-characterized molecular scaffolds. Such approaches could combine synthetic modification, computational prediction, and experimental validation in iterative cycles. Particular attention should be given to molecular stereochemistry, conformational flexibility, and the relationship between three-dimensional structure and biological recognition. The development of stereochemically informed molecular descriptors and more accurate computational models may help clarify relationships that are not captured by conventional two-dimensional structural analysis. At the same time, the synthesis of natural-product-inspired derivatives should be guided by practical considerations, including chemical accessibility, scalability, and the feasibility of further pharmaceutical development. The most promising compounds will not necessarily be those with the greatest structural complexity, but rather those offering a favorable balance among biological activity, selectivity, stability, and developability [20].

6.4. Improving Drug Delivery Without Losing Sight of Biological Relevance

Advanced formulations will continue to attract attention, particularly for natural compounds with limited solubility or unfavorable pharmacokinetic properties. However, the field would benefit from moving beyond formulation performance as an isolated objective.

The development of a new delivery system should begin with a clearly defined biological or pharmaceutical problem. If a compound is poorly absorbed, the formulation should be evaluated according to its ability to improve exposure. If instability is the principal limitation, the relevant outcome should be improved chemical or biological stability. If targeted delivery is proposed, evidence of preferential distribution and meaningful biological benefit is required. This problem-oriented approach may help reduce the development of technologically sophisticated formulations whose practical advantages remain uncertain. Future research should also consider manufacturing reproducibility, carrier-associated toxicity, and the feasibility of scaling up experimental formulations beyond laboratory conditions [21].

6.5. Developing More Informative Experimental Models

Another promising direction involves the use of experimental systems that better reproduce the complexity of living tissues. Three-dimensional cultures, organoids, microphysiological systems, and organ-on-chip technologies may provide additional information about compound behavior under conditions that more closely resemble physiological environments. These models are particularly relevant when cellular interactions, tissue architecture, or local biochemical conditions influence biological activity. Nevertheless, more complex experimental systems are not automatically more informative. Their value depends on whether they reproduce the biological processes relevant to the research question. A carefully selected combination of biochemical, cellular, tissue-based, and in vivo models may therefore be more useful than relying exclusively on any single experimental platform [22].

6.6. Connecting Molecular Responses with Functional Outcomes

An important future objective is to establish stronger relationships between molecular observations and functional biological outcomes. Changes in gene expression, enzyme activity, or inflammatory mediators can provide valuable mechanistic information, but they do not necessarily indicate improved tissue function or therapeutic benefit. For natural compounds proposed to influence inflammation, vascular function, tissue repair, or cellular proliferation, molecular measurements should ideally be accompanied by relevant functional endpoints. This could include assessments of tissue organization, cellular behavior, vascular function, metabolic activity, or physiological recovery, depending on the biological context. Such integration would help determine whether molecular changes represent meaningful biological effects rather than isolated experimental observations [23].

6.7. Reproducibility, Transparency and Responsible Innovation

The increasing sophistication of natural-product research also creates a responsibility to improve scientific transparency. Detailed analytical characterization, appropriate controls, reproducible experimental protocols, and transparent statistical reporting should be considered fundamental requirements rather than optional methodological improvements. Data sharing may further strengthen the field by allowing researchers to compare results, validate computational approaches, and avoid unnecessary duplication. Responsible innovation also requires consideration of the origin and sustainable availability of natural resources. The discovery of biologically valuable compounds should not depend on extraction practices that threaten biodiversity or create unsustainable demands on biological materials. Synthetic biology, microbial production platforms, and alternative manufacturing strategies may help address some of these challenges, particularly for compounds that occur naturally in limited quantities. The future of natural-product research should therefore be evaluated not only in terms of scientific novelty, but also according to reproducibility, sustainability, and practical feasibility [24].

7. Conclusions

Natural compounds remain an important source of ideas, molecular structures, and experimental opportunities for modern medicinal chemistry. Their continued relevance reflects both the diversity of natural chemical systems and the capacity of contemporary research methods to investigate them in increasingly sophisticated ways. At the same time, the field faces challenges that cannot be resolved through the discovery of additional bioactive molecules alone. Greater attention must be given to mechanistic validation, molecular optimization, pharmacokinetic behavior, reproducibility, and the relationship between experimental observations and meaningful biological outcomes. The Special Issue *"Research*

Progress and Application of Natural Compounds—2nd Edition" was designed to encourage research across these complementary areas and to promote a broader understanding of the scientific and practical potential of natural substances. Looking forward, artificial intelligence, multi-omics technologies, advanced molecular design, and improved drug delivery systems may help accelerate progress. Their contribution, however, will depend on rigorous experimental validation and effective collaboration across scientific disciplines. Perhaps the most important direction for future research is a change in emphasis: from asking whether a natural compound is biologically active to understanding why it is active, under which conditions its activity is relevant, and whether that activity can be translated into a meaningful application. We hope that the research brought together in this Special Issue will encourage further investigations along these lines and stimulate new collaborations between chemists, biologists, pharmacologists, and pharmaceutical scientists.

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