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RECEIVED 02 July 2025

ACCEPTED 29 September 2025

PUBLISHED 07 November 2025

CITATION

Pereira RC, Ramos YJ and Moreira DL (2025)
The eco-evolutionary *raison d'être* of natural
products as support for sustainable
bioprospecting.
Front. Ecol. Evol. 13:1658630.
doi: 10.3389/fevo.2025.1658630

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The eco-evolutionary *raison d'être* of natural products as support for sustainable bioprospecting

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Since time immemorial, a wide range of terrestrial, aquatic, and marine organisms have been used to treat illnesses and diseases, owing to the broad diversity of natural products they produce. Although widely recognized for their medicinal properties, natural products are fundamentally the result of adaptive chemistry - or phenotypic expression - of the organisms that produce them, shaped by evolutionary pressures from natural environmental enemies. This article examines natural products through ecological, evolutionary, and conservation lenses, highlighting how these perspectives add complexity to the already lengthy and costly process of bioprospecting. Due to their origin and evolutionary history, only a small fraction of the many screened natural products exhibits biological activity relevant to human health, as these compounds did not evolve to possess pharmacological properties. Our viewpoint emphasizes the true *raison d'être* of the vast diversity of natural products and argues that this perspective should be integrated into bioprospecting efforts. We propose focus on the ecological roles of natural products to offer a more rational, productive, and sustainable approach to drug discovery - one that aligns with biodiversity conservation and economic development.

KEYWORDS

secondary metabolites, bioprospection, chemical diversity, adaptive chemistry, biodiversity conservation

1 Introduction

Medicinal plants have supported human health for millennia, as evidenced by ancient records across cultures from Mesopotamia to China (Arya et al., 2022). Ethnobotanical traditions and early pharmacological texts document extensive plant-based treatments, while aquatic and marine organisms have also contributed bioactive compounds to traditional medicine (Jia et al., 2004; Aasim et al., 2019). Over time, the isolation of

plant secondary metabolites has led to major breakthroughs in treating cancer, infections, and neurological diseases, positioning natural products as vital resources in modern healthcare, pharmacology, and biotechnology (Papon et al., 2022; Labes, 2023; Rojo et al., 2023; Silveria and Boylan, 2023).

This article does not aim to provide a historical overview, but rather to reframe natural products not simply as drug leads, but as evolved adaptive traits shaped by ecological and evolutionary pressures. By highlighting their *raison d'être*, we argue for a shift toward a chemical ecology perspective - promoting sustainable, efficient, and biodiversity-informed bioprospecting.

2 Search strategy for scientific articles related to the *raison d'être* of natural products

To support our insights on the importance of considering the *raison d'être* of natural products in bioprospecting, a systematic search was conducted with the aim of answering the question: How has the integration of ecological and evolutionary approaches in marine, aquatic, and/or terrestrial bioprospecting contributed to the discovery of bioactive natural products with pharmaceutical potential? The methodological design followed the recommendations of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA, Moher et al., 2009) to ensure rigor, transparency, and reproducibility through stages such as identification, screening, eligibility, and inclusion of studies.

Data collection took place in August 2024 and used the following indexed 4 databases: PubMed/MEDLINE, Scopus, Web of Science, and SciELO/LILACS. The search strategy was structured using a combination of controlled descriptors and keywords in English, Portuguese, and Spanish, articulated by Boolean operators (AND/OR). The main terms used were: 'bioprospecting', 'natural products', 'metabolites', 'marine organisms', 'terrestrial plants', 'aquatic organisms', 'aquatic plants', 'chemical ecology', 'evolutionary approach', 'bioactive compounds', 'biotechnology', and 'pharmaceuticals'. A detailed description of the procedures used in the search (Supplementary Material) and workflow for selecting the relevant articles can be found in the Supplementary Material (Supplementary Table S1, Supplementary Material). Despite all the methodological rigor employed, it is not our intention to conduct a review, but rather to justify the innovative approach of the present perspective article.

The systematic search identified 115 records in the selected databases, PubMed/MEDLINE (n= 10), Scopus (n= 55), Web of Science (n= 49) and SciELO/LILACS (n= 1). After removing 29 duplicates, 86 records remained for initial evaluation. Of these, 14 studies were excluded for not meeting the minimum eligibility criteria. Thus, 72 records proceeded to the title and abstract screening phase, during which 24 were eliminated for not directly addressing bioprospecting or for not employing an ecological/evolutionary approach. In the full-text reading phase, 48 studies were assessed, with 24 excluded (4 due to being of an unsuitable study type and 20 for presenting a methodological approach outside the

defined scope). In the end, 24 studies were included in the systematic review and comprised the analysis corpus (Supplementary Table S2, Supplementary Material). However, none of these 24 articles (Supplementary Table S2, Supplementary Material) explored the purpose of natural products or the importance of considering their ecological roles and evolution in the bioprospecting of natural products. This finding underscores the relevance of our insight, emphasizing the importance of incorporating the *raison d'être* of natural products into bioprospecting.

3 General aspects on the development of pharmaceuticals

In the early stages of drug discovery, the process typically consists of two main steps: the collection of biological samples and the evaluation of its extracts for bioactivities. However, identifying promising biological activity is only the beginning of a long, expensive and complex process (Firn, 2003). Drug development is notoriously costly – estimate at approximately \$ 900 million – and can take around 14 years from discovery to market approval. Moreover, only a small number of potential candidates, referred to as “hits”, exhibit sufficient bioactivity to warrant further investigation as viable drug candidates (DiMasi et al., 2003). From these hits, a “lead” compound is selected for preclinical studies (Hunt and Vicent, 2006).

Screening of bioactive chemicals is generally conducted through one or more of the following approaches: (1) Random screening, (2) Ethnopharmacological knowledge or (3) The examination of chemical diversity within a particular taxon in comparison to another previously studied bioactive compounds. However, all these approaches, bioprospecting can lead to significative negative ecological consequences. For example, large-scale bioprospecting can lead to populations decline, loss of genetic diversity, genetic drift, and even local extinction of source species (DiMasi, 2001). These concerns raise important questions about the sustainability of a widespread biological sampling. Therefore, these bioprospecting strategies – whether random, ethnopharmacological, or taxonomically guided – may not always be environmentally sustainable.

In recent years, the advanced analytical tools such as Gas Chromatography-Mass Spectrometry (CG-MS) and/or Liquid Chromatography-Mass Spectrometry in tandem (LC-MS/MS), often combined with bioinformatics database resources like the Global Natural Products Social Molecular Networking (GNPS) have helped to mitigate these impacts (Cachet et al., 2015; Raina et al., 2022). These methods require only a few milligrams of material and allow for high throughput, environmentally conscious screening. Additionally, artificial intelligence and advanced *in vitro* technologies are being employed to streamline the drug development pipeline and reduce associated costs and timelines – though many challenges remain (Singh et al., 2023).

Once a promising compound is identified, however, the process of isolation and characterization represent a major bottleneck. Bioactive compounds are typically produced in very small quantities by their source organisms. For instance, several

marine-derived secondary metabolites - including ecteinascidin 743 from the ascidian *Ecteinascidia turbinata*, bryostatins from the bryozoan *Bugula neritina*, and halichondrins from the sponge *Lissodendoryx*, can only be isolated in trace quantities (Pereira and Costa-Lotufo, 2012). As a specific example, therapeutic use of halichondrins in cancer treatment would require 1–5 kg annually, which would necessitate harvesting between 3,000–16,000 metric tons of sponge biomass per year (Proksch et al., 2003).

In summary, although bioprospecting has led to important discoveries, its current models remain conceptually fragmented and environmentally unsustainable. The predominant reliance on random screening or ethnopharmacological knowledge often fails to incorporate ecological principles, leading to costly and low-yield outcomes. Moreover, these approaches typically overlook the adaptive nature of natural products, treating them as pharmacological candidates rather than evolved traits. This disconnect highlights the need for transdisciplinary frameworks that not only integrate chemical, biological, and ecological knowledge, but also reframe bioprospecting as a process informed by eco-evolutionary logic (Rotter et al., 2020). However, it is necessary and urgent that bioprospecting and its associated costs be minimized through the recognition of the true origin and evolution of natural products in the organisms that produce them.

Despite more than a century of research, many questions remain about the functions and ecological roles of natural products in the organisms that produce them (Dixon et al., 2024). But while the origin of secondary metabolites is not fully understood, it is widely accepted that they evolved to facilitate chemical defense, inter-organism communication, and competition within ecological communities. Thus, regardless of the procedure used in the search for bioactive substances, the origin and evolution of natural products cannot be disregarded, as this is the main foundation of our current insight.

4 Ecological and evolutionary views on the bioprospecting area

Among the major challenges in natural product bioprospecting is the low success rate in discovering new drug leads (Liu et al., 2019). For over two decades, bioprospecting has been viewed as economically discouraging due to high costs and the low probability that a given compound will display meaningful biological activity (Firn, 2003; Liu et al., 2019). However, in our view, a more fundamental limitation lies in the fact that natural products have evolved – through natural selection – to function primarily as chemical mediators in ecological contexts in the natural environments (terrestrial, marine, and aquatic), rather than as therapeutic agents for human use. For this simple reason, many molecules are tested, but only a small fraction exhibit biological activity. This outcome is not surprising if one considers that current screening strategies are largely blind to the ecological context in which natural products evolved. The assumption that any given metabolite might display therapeutic activity disregards its original adaptive function. This methodological oversight represents a critical limitation in traditional bioprospecting pipelines, which often

prioritize pharmacological potential over ecological relevance. A more productive strategy would reverse this logic, beginning with ecological function as a filter before pharmacological testing, thereby increasing both efficiency and sustainability.

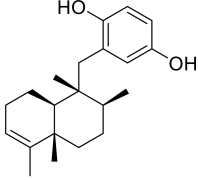
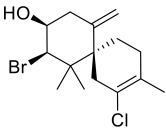
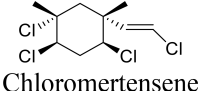
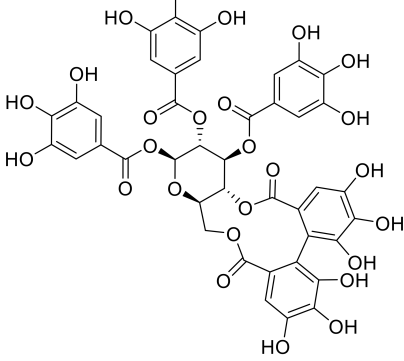
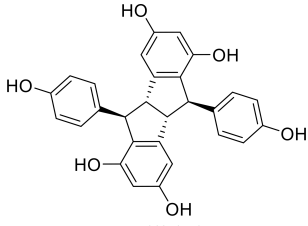
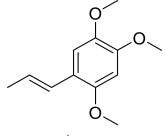
This idea is encapsulated in the known screening hypothesis, which suggest that potent biological activity is an uncommon property among natural products, given that most evolved to exhibit ecological roles rather than interact with human disease targets (Jones and Firn, 1991). This hypothesis was a pioneering attempt to conceptualize an evolutionary scenario in which significant constraints on the evolution of natural product diversity would have existed, given that most natural products did not possess a potent biological activity beneficial to the producer (Firn and Jones, 2003). As a result, bioprospecting screens tens of thousands of molecules, but only a small fraction shows promise as drug candidates. There is an evolutionary history behind the phenotypic expression of thousands of small molecules (natural products) that serve as chemical mediators in various ecological interactions among organisms and in their relationships with the environment. For many years, natural products have been repeatedly recognized as adaptive traits that have been shaped by natural selection during evolution (e.g. Wink, 2003; Erb and Kliebenstein, 2020). Assuming this is true, the organism that produce natural products have evolved distinct or unique types of these chemicals as selective response to numerous environmental factors or natural enemies. For example, the marine environments are significant variability in conditions such as pressure (1 atm for every 10 meters depth), salinity (salinities well below or above the average of 35), temperature (ranging from Antarctic waters and cold seeps to tropical regions and thermal vents), nutrient availability (from eutrophic to oligotrophic areas) and light, such as photic to aphotic zone (Rotter et al., 2021). It is therefore essential to consider the ecological rationale - or *raison d'être* - for the existence of these compounds when exploring their pharmacological potential. Unlike ecological functions, therapeutic activity in humans typically results from chance interactions, as most organisms producing natural products have not co-evolved with human pathogens or disease targets.

Contrary to ecological roles of evolved chemicals, biological activities may result from chance encounters, as most organisms have never had an evolutionary relationship with human diseases. Nevertheless, some biological activities help bridge the fields of bioprospecting and chemical ecology closer together. For this reason, studies on allelopathy have been suggested as promising avenues for the discovery and development of cytotoxic substances (Singh and Thakur, 2016), since this ecological role is often expressed through biological activities, such as: modification of membrane structure and transport receptors, changes in cell morphology, disruption of the cell cycle, altered phytohormone activity, disturbed energy metabolism, impaired water balance and stomata function, inhibited pigment synthesis, and blockage of key enzymes, especially regulatory ones. Chemicals from seaweeds (Alves et al., 2018) and marine sponges (Singh and Thakur, 2016) are known to influence cellular and biochemical processes, such as ATPase inhibition, microtubule stabilization, apoptosis, angiogenesis, migration and invasion. These biological activities have been observed in both *in vitro* and *in vivo* models, with some

manifesting as allelopathic effects. In Table 1, we include some examples of allelopathic substances from aquatic marine organisms and terrestrial plants, along with the biological activities they exhibit and, therefore, their defensive role against competition. More recently, a review highlighted several findings from marine

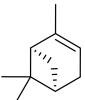
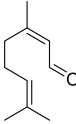
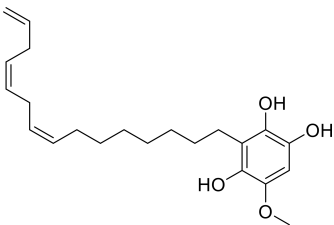
chemical ecology studies offer crucial insights for the sustainable discovery of new therapeutic pharmaceuticals (Tan, 2023). While these and other aspects are essential to advancing the field, they are not the only considerations. Bioprospecting must also incorporate evolutionary principles, as we discuss here. Objectively, it can

TABLE 1 Examples of ecological roles of allelochemicals derived from terrestrial and aquatic plants, as well as marine organisms, along with their modes of action in various biological activities.

Compound	Source	Organism type	Mode of biological action	Reference
 Avarol	<i>Dysidea avara</i>	Marine sponge	Superoxide production and single strand DNA damage. Inhibition of the signaling molecule eicosanoid, which regulates inflammation and suppresses superoxide generation. Inhibition of NF-κB translocation to the nucleus.	Ferrandiz et al., 1994; Müller et al., 1985, 1987.
 Elatol	<i>Laurencia</i> species	Red seaweed	Activation of autophagic and apoptotic cell death pathways induced by an imbalance in the parasite's redox metabolism.	Desoti et al., 2014.
 Chloromertensene	<i>Plocamium hamatum</i>	Red seaweed	Tissue necrosis.	De Nys et al., 1991.
 Tellimagrandin II	<i>Myriophyllum spicatum</i>	Aquatic Angiosperm	Inhibition of the PSII by interfering with the electron transfer.	Addisie and Medellin, 2012.
 Pallidol	<i>Carex distachya</i>	Aquatic Angiosperm	Toxic effect on plant germination	Fiorentino et al. 2008.
 α-Asarone	<i>Pistia stratiotes</i>	Aquatic Angiosperm	Inhibition of microalgae growth.	Alliota et al., 1991.

(Continued)

TABLE 1 Continued

Compound	Source	Organism type	Mode of biological action	Reference
 α -Pinene	Several plant species	Terrestrial Angiosperm plants	Oxidative stress to the plasma membrane and disruption of its structural integrity, ultimately leading to cell death.	Singh et al., 2016.
 Citral	Several plant species	Terrestrial Angiosperm plants	Effective in inhibiting seedling metabolism and photosynthesis, as well as suppressing adult plant growth and altering oxidative balance.	Graña et al., 2013.
 Sorgoleone	<i>Sorgum bicolor</i>	Terrestrial Angiosperm plants	Affects electron transport in both chloroplasts and mitochondria and acts as a potent in vitro inhibitor of photosystem II.	Dayan et al., 2009.

argue that natural products were not primarily selected to function as drugs for treating human diseases, despite being commonly evaluated for this purpose in bioprospecting research. Since natural products represent evolutionary and ecological responses to various environmental selective pressures, it is understandable why bioprospecting remains so costly; for example, 50,000 - 100,000 compounds may be required to obtain a single hit (Kuhlmann, 1997).

To illustrate this point, consider the example antifouling bioprospecting, which is considerably more efficient than drug discovery. Marine organisms such as seaweeds face similar selection pressures as man-made submerged structures (e.g., piers and boats) and have evolved natural antifouling compounds to deter colonization by epibionts. These compounds protect against threats that include reduced growth (Meichssner et al., 2020), impaired reproduction (Saier and Chapman, 2004), increased drag during storms (Dixon et al., 1981), and higher susceptibility to consumers (Da Gama et al., 2008). Thus, antifouling compounds offer a clear case of evolved chemical function aligned with potential applied use, demonstrating the benefit of integrating ecological understanding into bioprospecting.

The concept of integrating bioprospecting with chemical ecology is not entirely new. For instance, Ledoux and Antunes (2018) proposed a functional workflow that prioritizes the ecological roles of marine natural products before chemical identification, in order to narrow the existing gap between the growing number of known these chemicals and the limited understanding of their ecological roles. However, what we emphasize here is the pressing need to take into account the origin and evolution of natural products in bioprospecting initiatives, given the various aspects highlighted in this discussion. Moreover, understanding the mechanisms and evolutionary pathways underlying the occurrence of natural

products in nature will ultimately enable the efficient bioengineering of desirable metabolic traits in the organisms that produce them (Weng et al., 2021).

However, we are not aware of bioprospecting approaches that emphasize the fact that natural products are adaptive chemistry - phenotypic expressions of the species that produce them. Over the course of the evolution, genes encoding enzymes involved in primary metabolism have been duplicated, recruited, and diversified to perform new functions in response to the ever-changing selective pressures of the environment (Hartmann, 2007). Therefore, for these evolutionary reasons, a metabolite that exhibits an ecological role will not necessarily exhibit biological activity (such as anti-cancer or anti-viral effects); on the contrary.

5 Concluding remarks – future perspectives and limitations

Undoubtedly, bioprospecting efforts have expanded our understanding of the vast chemical diversity produced by terrestrial, marine, and aquatic organisms. However, only a small fraction of this diversity has had its ecological role elucidated. If, instead of focusing predominantly on drug discovery, bioprospecting efforts over the past decades had been directed toward understanding the ecological roles of these compounds, we might today possess deeper knowledge of how these chemicals operate at multiple levels - from cells to entire ecosystems. Such understanding could have provided critical scientific support for biodiversity conservation of across global ecosystems.

Bioprospecting has long been heralded as a dual solution for drug discovery and biodiversity conservation. However, this narrative has proven overly optimistic. In practice, the economic and ecological costs of current strategies often outweigh their benefits, and industry

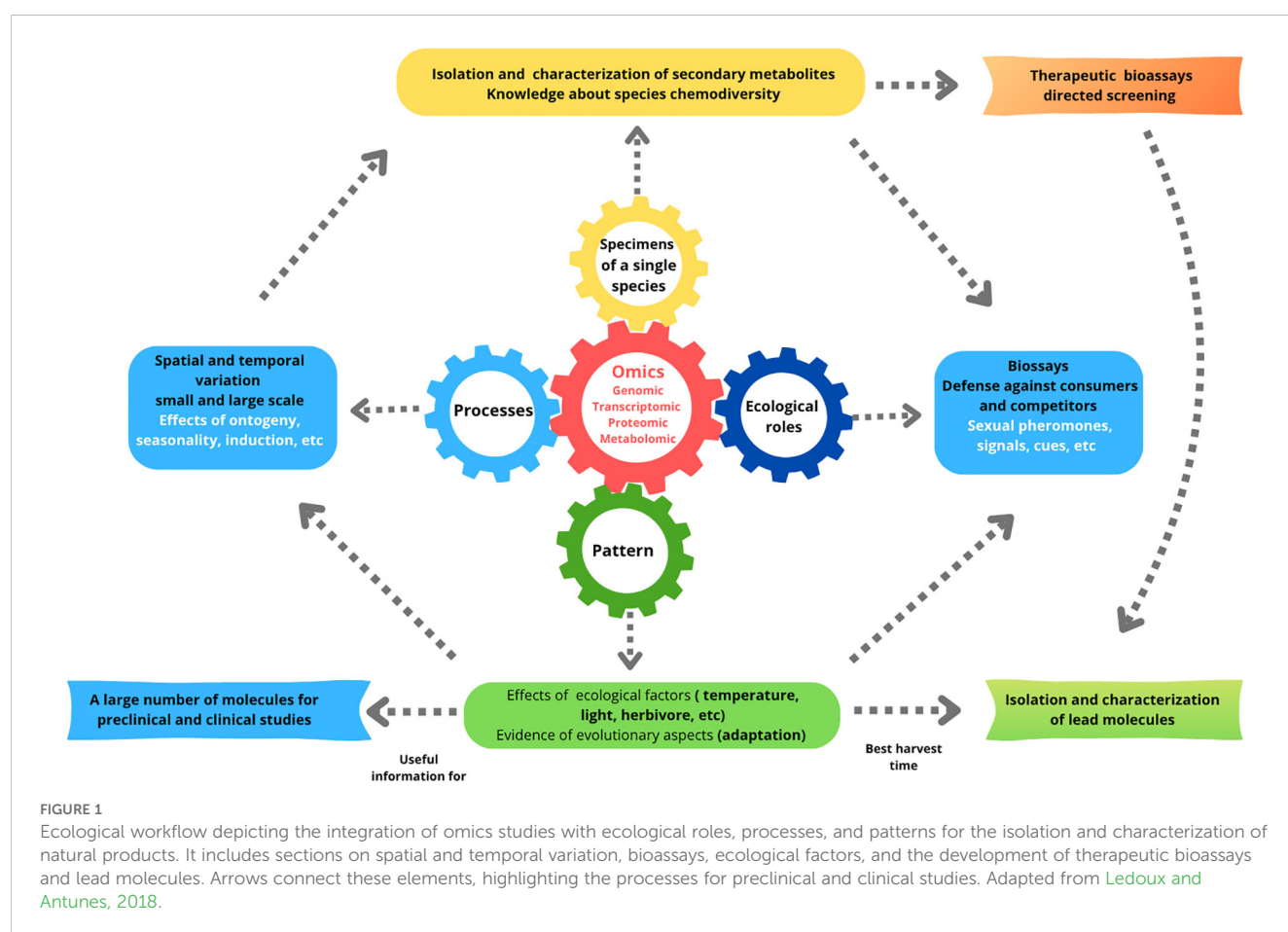
investment remains minimal. This disconnect stems largely from the failure to critically assess the ecological foundations of natural product diversity. Without a conceptual shift (one that recognizes natural products as evolved chemical traits rather than mere repositories of bioactivity) the full potential of biodiversity will remain underexploited and poorly protected (Firn, 2003).

Considering the reasons that separate and connect chemical ecology and bioprospecting areas, we argue that there are strong reasons for integrating them. Some key reasons include: 1) Improved cost/benefit ratio, as investigating ecological roles may lead to more positive outcomes; 2) Bridging the gap between the number of known metabolites and the understanding of their ecological roles; 3) Lowering research costs, as a single metabolite could be tested both for biological activity and ecological roles, making one organism or collection serve dual purposes and increase the meaningful results through ecological “screening”; 4) Ecological Investigation can provide libraries of chemicals (e.g., Nocchi et al., 2017) that may later be explored for pharmacological and other biological properties (e.g., Desoti et al., 2014). Thus, a workflow that integrates ecological approaches - either prior to or alongside traditional bioprospecting methods (see Figure 1) - could be both scientifically productive and mutually beneficial for the fields of bioprospecting and chemical ecology.

Reflecting on the bioprospecting strategy proposed here, we suggest that screening based on the ecological roles of secondary metabolites

represents a more rational and strategic alternative to conventional bioprospecting approaches. Moreover, this approach has the potential to foster sustainable development and biodiversity conservation while also supporting the economic development of biodiversity-rich countries.

While we argue that integrating eco-evolutionary reasoning into bioprospecting is a promising avenue, this approach is not without its challenges. One limitation lies in the current lack of standardized methodologies to systematically evaluate the ecological roles of natural products *in situ* or in complex community contexts. Furthermore, many organisms remain poorly studied from an ecological perspective, particularly in marine and microbial ecosystems, limiting our ability to formulate predictive frameworks. The development of functional ecological assays, metabolomic databases annotated with ecological metadata, and interdisciplinary collaborations will be critical to advance this field. Additionally, scaling this approach requires institutional support, funding mechanisms, and training in chemical ecology, areas that remain underrepresented in many bioprospecting programs. Nevertheless, the convergence of ecological theory, evolutionary biology, and chemical analytics offers a fertile ground for reimagining natural product discovery. Future research should focus on validating ecological screening models, developing bioinformatic tools for ecological annotation, and assessing the conservation implications of targeting ecologically functional compounds.



Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author/s.

Author contributions

RP: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. YR: Visualization, Conceptualization, Writing – review & editing. DM: Methodology, Conceptualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This study was partially supported by Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), through the “Scientist of the State” Program for RCP and DLM, grants (Proc. E-26/201.141/2022 and E-26/201.211/2022), respectively. RCP and DLM also thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for their Research Productivity Fellowships (Proc. 306417/2025-1 and 306861/2023-2, respectively). YJR thanks the Federal University of Bahia for the Young Researcher Fellowship (PRPPG 010/2024).

Acknowledgments

The authors express their gratitude to their institutions (Federal Fluminense University, Federal University of Bahia, and Rio de Janeiro Botanical Garden Research Institute, Rio de Janeiro, Brazil) for providing the administrative and research support necessary to conduct this study.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fevo.2025.1658630/full#supplementary-material>

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