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COMMENTARY

Biodiversity2Drugs—Renaissance of exploring nature-derived peptides for GPCR ligand discovery

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Abbreviations: AI, artificial intelligence; B2D, Biodiversity2Drugs consortium.

GPCR drug discovery from nature—G protein-coupled receptors (GPCRs) are a cornerstone of therapeutic innovation, representing the largest and most versatile family of drug targets in the human body (Lorente et al., 2025). These receptors play a crucial role in regulating nearly all physiological processes, making them essential targets for addressing a wide range of conditions, from metabolic disorders to cancer. Nature-derived small molecules and peptides have been fundamental for the development of many successful GPCR therapeutics (Muratspahić et al., 2019). Morphine, originally derived from the poppy plant *Papaver somniferum*, was one of the first GPCR ligands to be found in nature and continues to play a vital role in managing both chronic and acute pain. For example, **angiotensin-converting enzyme** inhibitors in clinical use to treat hypertension were originally derived from peptides found in snake venom. Exendin-4 is a venom peptide found in the saliva of the lizard *Heloderma suspectum*, which was the first incretin-based drug to be approved, owing to its improved stability over endogenous **GLP-1**. It paved the way for the development of next-generation GLP-1 receptor agonists such as semaglutide, now widely used for the treatment of type 2 diabetes and obesity. These transformations of biomolecules into life-saving drugs underscore the potential of natural peptides as blueprints for the next generation of GPCR-targeted drug discovery efforts.

The newly formed Biodiversity2Drugs (B2D) consortium (www.biodiversity2drugs.com) leverages terrestrial and aquatic biodiversity to systematically explore bioactive peptides refined by millions of years of evolution. These peptides offer potential potency and specificity for interacting with cellular receptors such as GPCRs, which regulate key signalling pathways linked to inflammation, pain, cancer, and metabolic diseases (Muttenthaler et al., 2021). Initiated to enable sustainable mining of nature's molecular repertoire to identify novel therapeutic leads, B2D unites >25 partners from diverse disciplines in a collaboration across 18 countries. With emphasis on GPCRs, B2D is focused on exploring the need for discovering drug candidates with greater efficacy, improved specificity and higher selectivity.

As recently highlighted in a themed issue of the British Journal of Pharmacology, the latest efforts in GPCR structural studies and ligand development have been spurred by progress in employing cryo-electron microscopy (EM), nuclear magnetic resonance (NMR) spectroscopy, and artificial intelligence (AI)-assisted protein structure prediction (reviewed by Kogut-Günthel et al., 2024). Applying these tools enabled important insights into GPCR activation, ligand binding, dimerization and signalling pathways. Although it is still challenging to harvest the results of such studies given the complexity of dynamic receptor conformations and interactions, the authors emphasize the need for integrating structural and biophysical techniques with computational tools to fill gaps in the characterization of the diversity of GPCR activation states and dynamic landscapes towards improved drug discovery. In this context, peptide ligands (including those isolated from natural sources) offer great potential as molecular probes for elucidating GPCR characteristics. Peptides (especially nature-derived and stabilized peptides) can exhibit unique binding modes and higher selectivity, as compared to small molecules. As ideal tools for characterizing receptor conformations, peptides offer motifs suitable for computational approaches. Peptides can enable the refinement of structural predictions and reveal previously inaccessible features of GPCR-ligand interactions. Aiming to combine structural biology with biodiversity-inspired ligand discovery, B2D is positioned to expand the development of GPCR-targeted ligands by exploring a diverse structural landscape.

Another review by Morales et al. (2024) examined biased modulation and functionally selective signalling of GPCRs, and implications for discovery of ligands that preferentially activate specific signalling pathways by stabilizing distinct receptor conformations. Discovery of such ligands has the potential to reduce adverse effects associated with traditional GPCR ligands, offering safer and more precise therapeutic options. The review catalogues recent progress in identifying biased ligands across various GPCR families (focusing on class A receptors), emphasizing therapeutic relevance and molecular determinants for activity. In this context, B2D aims to discover natural peptides, which can serve as starting points for the design of biased ligands. Many natural peptides have evolved to interact with GPCRs in ways that confer functional selectivity, sometimes acting as biased or allosteric modulators. This provides a strong basis for exploring natural peptide diversity for GPCR ligand discovery. By leveraging the B2D partnership, we aim to identify novel peptide ligands that can modulate GPCR function. This approach will allow B2D to demonstrate the value of biodiversity and contribute to the development of more selective and potentially safer GPCR-targeted peptide therapeutics.

Biodiversity has long served as an invaluable reservoir for drug discovery. Over 40% of pharmaceuticals are derived from natural sources. Bacteria and fungi have yielded antibiotics and statins. Plants like the yew tree *Taxus brevifolia* have provided essential anticancer agents like paclitaxel (originally named taxol). Aspirin, one of the most widely used drugs, is derived from the bark of the willow tree. In fact, 70% of anticancer drugs have natural or bioinspired origins. Importantly, the very beginning of GPCR pharmacology can also be traced to compounds originating from plants and fungi, such as, muscarine, atropine, and the ergot alkaloids. In recent decades, nature-derived peptides have entered the spotlight as powerful drug candidates, particularly those from animal venoms. For example, **ziconotide**, a peptide originally isolated from the cone snail *Conus magus*, is used in the treatment of severe chronic pain. These examples emphasize the potential and need for further exploration of natural products for drug discovery (Muratspahić et al., 2019).

Biodiversity loss driven by climate change and habitat destruction threatens valuable resources of molecular diversity. Natural products come from an astonishing diversity of species that spans bacteria, fungi, plants, animals (invertebrates and vertebrates), and others. Figure 1 highlights the estimated number of species in three major groups and reinforces the critical importance of conservation for drug discovery. Investing in sustainable bioprospecting ensures the discovery of novel drug candidates. Huge economic and societal benefits can be fostered by preserving ecosystems. By harnessing nature's 'pharmacopoeia', B2D aims to deliver innovative drug-like molecules and biodiversity conservation alike.

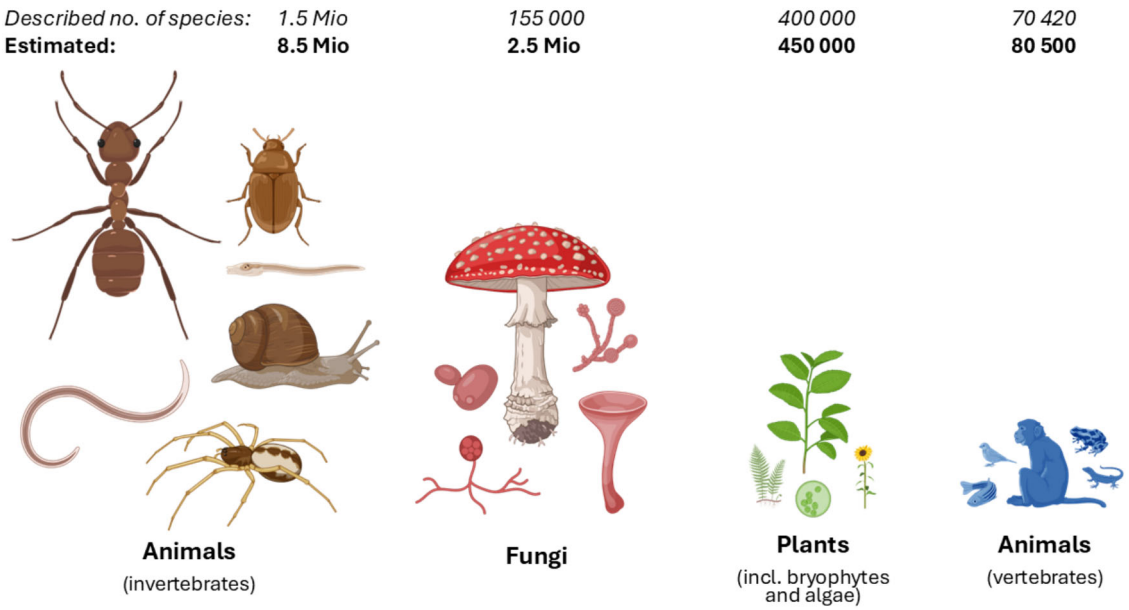

FIGURE 1 The figure illustrates species diversity across three kingdoms of life: fungi, plants, and animals (with vertebrate and invertebrate animals depicted separately). The described (italicized) and estimated (bold) no. of species for each group are provided as numbers above the illustration. Despite not explicitly included in the outline, bacteria with their immense and largely unexplored diversity, represent a rich reservoir of bioactive peptides. The figure has been adapted and modified from the World Economic Forum (23/11/2023; this is how biodiversity loss impacts medicine and human health; https://www.weforum.org/stories/2023/11/biodiversity-nature-loss-health-medicine/) with data sources and references used for its compilation provided by Niskanen et al. (2023). The figure was created using the help of Biorender.

Through innovative workflows and methods utilizing genomics, transcriptomics, peptidomics, and AI/machine learning (ML)-aided computational tools, B2D primarily focusses to uncover novel GPCR ligands and enhance our understanding of GPCR signalling and structure–function relationships. Peptides, in contrast to small molecules, are generally associated with lower toxicity due to their composition from natural amino acid building blocks and their larger molecular size, which promotes higher target specificity and minimizes off-target interactions. Their extended molecular surface allows for more diverse and selective engagement with receptor sites, often enabling alternative modes of pharmacological action. Nonetheless, the clinical translation of peptide therapeutics remains hindered by poor oral bioavailability, limited metabolic stability, and inadequate cell and blood–brain barrier permeability. Advances in medicinal chemistry—including the design of peptidomimetics and macrocycles, particularly those inspired by natural scaffolds—offer promising avenues to address these limitations and realize the full therapeutic potential of peptide-based drugs.

By exploring peptides in their evolutionary and ecological contexts, B2D seeks to uncover bioactive molecules with therapeutic potential. Integrating ecological knowledge with pharmacological expertise and computational approaches, B2D may help to address key health challenges such as pain, autoimmune and cardiovascular diseases, diabetes, obesity, and cancer. Sustainability is a guiding principle, with an emphasis on environmentally responsible sampling and scalable production methods. In the long term, the initiative aims to build a collaborative network across academia, industry, and policy to support innovation at the intersection of drug discovery and biodiversity research. B2D highlights the value of the Biodiversa+ (www.biodiversa.eu) theme 'Nature-Based Solutions' in addressing both medical and environmental challenges.

Nomenclature of targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander, Christopoulos et al., 2023; Alexander, Fabbro et al., 2023).

The Biodiversity2Drugs Consortium

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CONFLICT OF INTEREST STATEMENT

Nicolas Gilles co-founded V4Cure. All other authors declare no conflict of interest.

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