Plant-Derived Peptides: (Neglected) Natural Products for Drug Discovery#

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ABSTRACT

Peptides have emerged as key regulators in various physiological processes, including growth, development, stress, and defense responses within plants as well as ecological interactions of plants with microbes and animals. Understanding and harnessing plant peptides can lead to the development of innovative strategies for crop improvement, increasing agricultural productivity, and enhancing resilience to environmental challenges such as drought, pests, and diseases. Moreover, some plant peptides have shown promise in human health applications, with potential therapeutic benefits as ingredients in herbal medicines as well as novel drug leads. The exploration of plant peptides is essential for unraveling the mysteries of plant biology and advancing peptide drug discovery. This short personal commentary provides a very brief overview about the field of plant-derived peptides and a personal word of motivation to increase the number of scientists in pharmacognosy working with these fascinating biomolecules.

Peptides are a molecule class of growing interest to the natural products community. They have been identified and isolated from microbes, fungi, plants, and animals [1, 2]. Besides a small number of nature-derived peptides that are being enzymatically synthesized, most of them are gene derived. These so-called ribosomally synthesized and post-translationally modified peptides (RiPPs) can be discovered at the transcriptome or genome level [3]. Hence, with an ever-growing number of available genetic information, the discovery of novel peptide natural products is on the rise. For instance, the 1000 plant transcriptomes initiative (1KP) [4] and the ongoing 10 000 plant genomes sequencing project (10KP) [5] provide a unique platform of data for the discovery of RiPPs in plants. This led to studies about the biodiversity, evolution, and biosynthesis of plant-derived peptides [6, 7], as well as many exciting discoveries about their biological activity and application(s) in drug discovery [8]. This ongoing trend in plant peptide investigations is further documented by the increasing number of available databases and online collections dedicated to the curation of plant-derived peptides, such CyBase [9], PlantAFP [10], PlantPepDB [11], and PhytAMP [12].

The first plant peptide discovered was (puro)thionin from wheat in the 1940 s [13], which is a representative defense peptide found in grain seeds and many other plants [14]. The first

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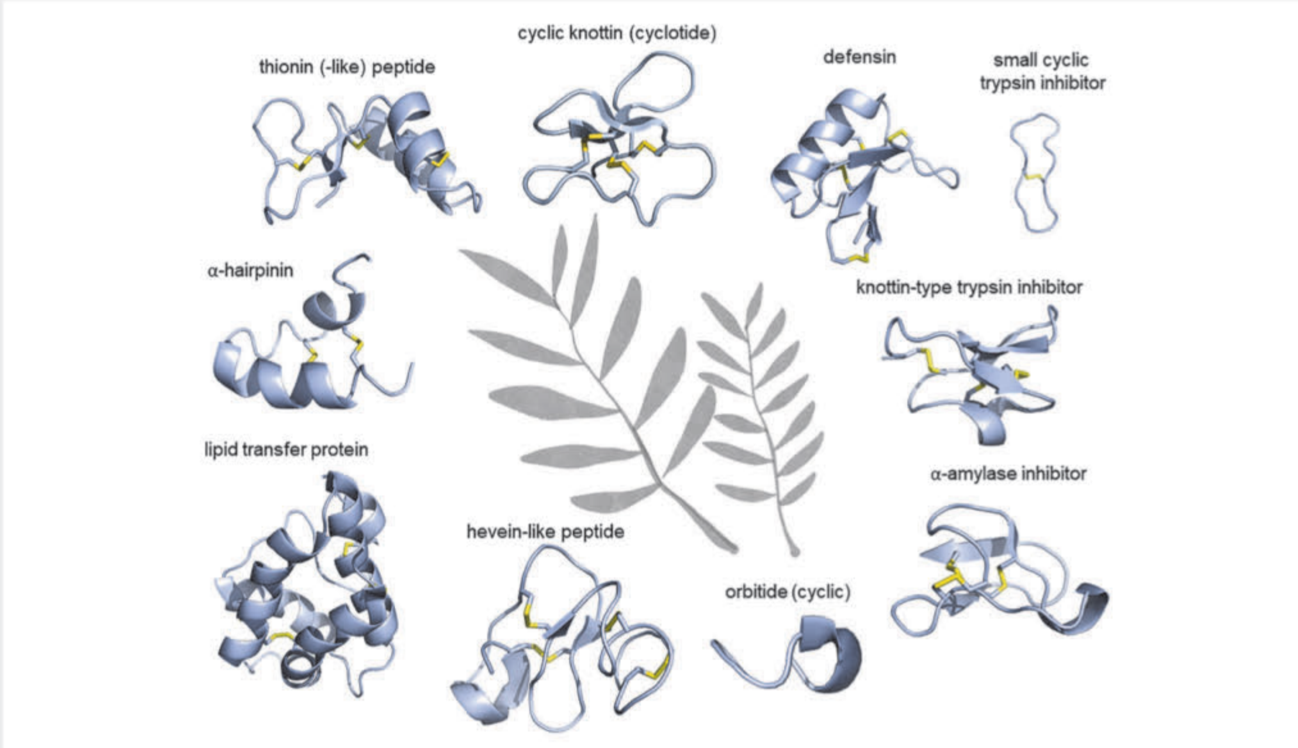

▶ **Fig. 1** Structural diversity of plant peptides. Compilation of structural cartoons of representative members of different classes of plant-derived peptides. Exemplarily shown are: cyclotide – a cyclic knottin – from *Oldenlandia affinis* DC. (pdb code: 1NB1), a small cyclic trypsin inhibitor from *Helianthus annuus* L. (1JBL), a thionin(-like) peptide from *Viscum album* L. (1ED0), a defensin from *Nicotiana alata* Link & Otto (1MR4), an α-amylase inhibitor from *Amaranthus hypochondriacus* L. (1QFD), a knottin-type trypsin inhibitor from *Ecballium elaterium* (L.) A.Rich. (2IT7), an α-hairpinin from *Hordeum vulgare* L. (2M6A), a lipid transfer protein from *Pisum sativum* L. (2N81), a hevein-like peptide from *Gypsophila vaccaria* (L.) Sm. (5XDI), and orbitide (cyclic) from *Jatropha ribifolia* (Pohl) Baill. (6DKZ). Disulfide bonds are shown in yellow.

plant peptide hormone discovered was systemin from tomatoes in 1991 [15]. Formerly, the isolation and structural characterization of these peptides must have been a laborious task, but nowadays there are multiple peptidomics workflows for fast and reliable mining of peptide sequences [1]. Over the years, several different classes of plant peptides have been described and characterized, displaying a unique diversity of sequences and three-dimensional folds (▶ **Fig. 1**) [1, 14, 16]. It is sheer impossible to determine the exact number of existing plant peptides, but given their physiological importance, structural diversity, and kingdom-wide distribution there must be millions, most of them yet to be discovered. This provides unique opportunities for the exploration of plant peptides for biology and drug discovery.

At a more general level, peptides appear to be ideal lead molecules for drug development since they combine the best features of "classical" small molecule drugs and "modern" biologics [17]. The number of peptide drugs approved by the US Food and Drug Administration (FDA) has steadily been growing. From 2016 to 2022, there have been 315 new drugs approved, of which 26 were peptides and 140 small molecules [18]. This equates to 8.3% of peptide drug vs. 44.4% small molecule drug approvals. Obviously, the total number of new small molecule drug approvals is still higher, but the approvals of new peptide drugs will continue to increase knowing that there are over 1000 peptides in various stages of clinical development [17, 19].

Although the quantity and structural diversity of peptides to be found in plants is unprecedented, they appear to play a subordinate role in the pharmacognosy communities as compared to small molecules. This is documented by the low number of manuscripts with "peptide-related" content that are being published, for instance, by Planta Medica, i.e., traditionally linked to the central European Pharmacognosy communities, and the leading journal of the Society for Medicinal Plant and Natural Product Research. In Planta Medica, only 0.6% of manuscripts reported a peptide or peptide-related study (i.e., 64 of a total of 10441 manuscripts indexes in PubMed since 1961) (▶ **Table 1**). In comparison, the Journal of Natural Products – traditionally linked to the American Chemical Society and the American Society of Pharmacognosy – published 3.4% of its manuscripts on peptide-related topics, and the Journal of Biological Chemistry even published approximately 1 in 10 papers about "peptides" (▶ **Table 1**). Other plant-related journals, such as Phytochemistry (2.5%) and Plant Cell (3.3%), or the major interdisciplinary journal Nature (1.4%), publish at least twice to four times as many peptide papers compared to Planta Medica (▶ **Table 1**). For reference, the Journal of Peptide Science – the official journal of the European Peptide Society – published over 86% of manuscripts about pep-

▶ **Table 1** Numbers of published "peptide-related" articles across various journals.

Journal	Total no. articles indexed*	Period of search	"Peptide" articles[#]	[%][§]
Planta Medica	10441 (incl. 398 reviews)	as of 1961	65 (incl. 8 reviews)	0.6
Journal of Natural Products	11832 (351)	as of 1979	401 (24)	3.4
Phytochemistry	8563 (500)	as of 1991	210 (16)	2.5
Plant Cell	8580 (298)	as of 1989	282 (7)	3.3
Nature	130136 (1283)	as of 1945	1871 (17)	1.4
Journal of Biological Chemistry	184639 (1746)	as of 1945	20075 (65)	10.9
Journal of Peptide Science[%]	2354 (180)	as of 1995	2034 (159)	86.4

*Numbers are based on a PubMed (https://pubmed.ncbi.nlm.nih.gov/) search on September 5, 2023; [#]search term: "peptide" [Title/Abstract] OR "peptidic" [Title/Abstract] OR "peptides" [Title/Abstract] OR "peptide" [Title/Abstract]) AND "*journal name*" [Journal]; [§]calculation of percentage is based on total number of articles (including reviews); [%]listed as reference

tides, according to the search criteria as outlined in the footnotes of ▶ **Table 1**.

Arguably, this analysis may not be representative, and there are only a few journals that were considered here. Nevertheless, the points to be made are that

- (i) peptides are fascinating molecules and display a rich biodiversity in plants,
- (ii) peptides are important molecules in drug discovery,
- (iii) the pharmacognosy community and the readership of Planta Medica are (becoming to be) experts in the isolation and characterization of bioactive molecules from plants and,
- (iv) many medicinal plants and plant species that are being extracted day by day in pharmacognosy laboratories contain peptides, yet only very few papers about peptides are being published in Planta Medica. Why?

I will not attempt to explain this discrepancy, but clearly there are missed opportunities when considering the abundance and distribution of plant peptides and availability of extraction protocols and analytical tools in many modern pharmacognosy laboratories. I have no doubt about the appreciation of plant-derived peptides by the pharmacognosy community but would like to raise awareness and spread motivation to everyone in the pharmacognosy community to consider or continue working with peptides, alongside established projects on small molecules. This could include the isolation of novel peptides with hitherto unknown biological function [20, 21], or the use of peptides as biomarkers and reference compounds for herbal quality control [22].

Examples of plant-derived peptides that have advanced into development for crop improvement or human health include the following:

- Pezadeftide, a plant-derived antifungal peptide – originally isolated from the bitterbush *Picramnia pentandra* – currently in clinical trials for therapy of onychomycosis or fungal nail infections (under development by Hexima, Australia) [23].
- T20K, a plant-derived circular peptide – originally isolated from the Rubiaceae *Oldenlandia affinis* – which is in clinical trial as a drug for multiple sclerosis (under development by Cyxone, Sweden) [24].
- Sero-X, the world's first peptide-based plant extract botanical pesticide developed from the butterfly pea (*Clitoria ternatea*) [25] (marketed by AgInnovate, Australia).

In summary, plant peptides comprise a unique chemical space that can readily be explored using modern peptidomics tools [1] and/or phytochemistry protocols that are available to many researchers in the pharmacognosy community. Peptides of different structural classes are (underestimated) components of herbal drugs or plant-based foods or medicines such as Violae [6], Beta [7], Sambuci [26], or Visci [27]. So please spread the word, to "make peptides great (again)!"

Disclaimer

Parts of this manuscript reflect the opinion solely of the author. No offence to anyone with a different viewpoint.

Contributors' Statement

C. W. G. performed the literature survey, drafted, wrote, and approved the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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