Bioactive Molecules from Plants: Discovery and Pharmaceutical Applications

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The plant kingdom is one of the richest sources of bioactive compounds with pharmaceutical potential. A special feature of higher plants is their ability to produce a great number of secondary metabolites of a high chemical diversity. Plants are also enriched in a wide variety of diverse proteins, peptides, sugars and nucleosides, which are often involved in plant primary physiological functions and/or in mechanisms against pathogens. These compounds can be widely found in fruits, seeds, flowers and leaves, from where they can be extracted and purified by different techniques. For decades, a plethora of bioactivities have been found in molecules isolated from plants, and they are still one of the leading sources of novel bioactive compounds. This editorial aims to summarize the 33 articles (27 research articles, 3 communications and 3 reviews) that contributed to the first edition of this Special Issue ‘Bioactive Molecules from Plants: Discovery and Pharmaceutical Applications’. The original research contributions included herein address the identification and characterization of novel molecules with a wide spectrum of biological activities. The Special Issue also includes several original reports describing the encapsulation and delivery of plant-derived compounds. In the following sections, we review all the articles in our Special Issue, and we believe this editorial will be of interest to a broad readership in the field.

Many plant-derived compounds have been used in the past because of their antimicrobial properties. Four studies in this Special Issue report the characterization of novel bioactive molecules and plant-derived biopolymers with strong antimicrobial properties [1–4]. Plants are also an important source of antioxidant peptides. In this volume, three publications investigated the antioxidant and ROS scavenging properties of plant-derived molecules [1,5,6]. Two of these studies by Cotabarren et al. have also shown the isolation and characterization of thermostable peptides with anticoagulant properties [2,6]. In addition, the study of Lee et al. has shown the identification of a bioactive natural product with potential anti-inflammatory activity [7]. The article from Tavares et al. studied the effect of the essential oil of *Cymbopogon winterianus*, a natural product with antioxidant, anti-inflammatory and antifibrotic properties, in the progression of histological changes of pulmonary fibrosis in a rodent model [8]. The article of Abdalla et al. drives us more into the importance of plant nutrition. They applied metabolomic approaches to investigate the effects of sulfur nutrition on the metabolic profiles and biological activities of three different *Lactuca sativa* (lettuce) cultivars [9].

Probably plants are the most well-known source of molecules with demonstrated anticancer therapeutic properties. Another set of papers of this Special Issue have investigated the antitumoral properties of plant extracts and plant-derived compounds, revealing interesting antiproliferative and/or pro-apoptotic activities in vitro [10–18]. In addition, Huang and coworkers have shown that Ceylon olive leaf extract and its phytochemicals, such as...
mearnsetin, displayed potent antimelanogenesis effects in a zebrafish model [19]. Many of these studies have provided key mechanistic insights into their specific biological functions.

In this Special Issue, we also expanded our knowledge on plant-derived compounds with a role in modulating key targeted cellular signaling pathways. An interesting study by Bertozzi and coworkers has shown that taro lectin can promote immunomodulatory effects by acting as a cytokine-mimetic compound [20]. On the other hand, Lee and coworkers reported that schisandrol A exhibits estrogen-like properties by promoting estrogenic activity via the estrogen receptor α-dependent signaling pathway [21]. Additionally, two studies have been conducted to investigate the antidiabetic properties of naturally occurring molecules from plants. The first work by Caroleo et al. showed that olive oil lipophenols can induce insulin secretion in an in vitro β-cell model [22]. The second study led by Lim et al. suggests that two flavonoids isolated from Morus alba fruits have the potential to promote insulin-stimulated glucose uptake in 3T3-L1 adipocytes [23]. Together, these two works indicate that bioactive molecules from plants can be potentially exploited for glycemic regulation in the management of type 2 diabetes mellitus (T2DM).

Increasing evidence indicates that compounds derived from some plants have a role in neuroprotection. Two articles of this Special Issue focused on the utilization of plant-derived compounds as neuroprotective [24] or neuromodulatory [15] agents. In the first of such studies, Meganova and coworkers evaluated the effects of novel hydroxamic acid derivatives in a 5xFAD transgenic mice model of Alzheimer’s disease (AD). Notably, one of the leading compounds was able to restore normal memory functions to the level observed in control wild-type animals [24]. In the second study, contributed by De Oliveira et al. to this Special Issue, the authors investigated the effects of saffron extract pre-treatment for prevention of stress-induced depressive-like behaviors [25]. Taken together, these studies highlight the potential of compounds derived from plants for the prevention and treatment of AD and other neurodegenerative diseases.

In the last couple of decades, numerous methods for the encapsulation of plant-derived molecules have been developed for drug delivery purposes. It has been increasingly recognized that this approach is useful to improve the solubility, biodistribution and successful delivery of naturally occurring molecules. This Special Issue also includes selected contributions addressing this topic. For example, Landucci et al. reported the fabrication of two liposomal formulations developed for the efficient encapsulation of thymoquinone, a phytochemical compound found in the seeds of Nigella sativa. They demonstrate the efficacy of these preparations, achieving improved ocular delivery of this compound [26]. Moreover, a publication by Magalhães et al. has shown that the essential oil nanoemulsion substantially improved its inhibitory activity [27]. Hydrogels also appear to be an excellent approach for controlled drug delivery. Along this line, Batista et al. presented a new thermosensitive hydrogel topical formulation containing Viscum album (mistletoe) extracts [28]. An additional publication explored the incorporation of cyclodextrin during resveratrol extraction. By using this approach, the authors improved resveratrol solubility, which at the same time enhanced mucoadhesive properties of the final formulation [29]. In the same direction, a comprehensive study by Kobryń and coworkers investigated the optimal solvent conditions for dermal hydrogel formulations with cryptotanshinone [30].

The last three contributions of this Special Issue constitute a collection of high-quality updated reviews. The first review written by Lupaescu et al. covers the role of various small bioactive molecules known to ameliorate amyloidosis [31]. They also discuss the link between these compounds and the prevention and development of T2DM and AD. The second review contributed by Filipiuc et al. dissects current findings on phytocannabinoids, including a detailed description of their cannabinoid and non-cannabinoid receptors [32]. The third review submitted by Manganyi et al. is a critical review summarizing current roles of therapeutic and toxic compounds derived from Drimia species [33].
In conclusion, the publications in this research topic highlight the diverse current efforts in identifying novel molecules derived from plants, providing a detailed view of the field, from compound identification to their therapeutic use.

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**References**

1. Forzia, F.; Shaheen, A.; Ahmad, I.; Amin, S.B.; Ahmad, N.; Ullah, R.; Bari, A.; Sohaib, M.; Hafiz Majid, M.; Aloibaid, A. Balliodiolic Acid A and B: Two New ROS, (•OH), (ONOO−) Scavenging and Potent Antimicrobial Constituents Isolated from *Ballota pseudodictamnus* (L.) Benth. *Pharmaceutics* 2021, 13, 402. [CrossRef]

2. Cotabarren, J.; Claver, S.; Payrol, J.A.; Garcia-Pardo, J.; Obregon, W.D. Purification and Characterization of a Novel Thermostable Papain Inhibitor from Moringa oleifera with Antimicrobial and Anticoagulant Properties. *Pharmaceutics* 2021, 13, 512. [CrossRef] [PubMed]

3. Neto, I.; Domínguez-Martín, E.M.; Ntungwe, E.; Reis, C.P.; Pesic, M.; Faustino, C.; Rijo, P. Dehydroabiatic Acid Microencapsulation Potential as Biofilm-Mediated Infections Treatment. *Pharmaceutics* 2021, 13, 825. [CrossRef] [PubMed]

4. Merlani, M.; Scheibel, D.M.; Barbakadze, V.; Goglashvili, L.; Amiranaishvili, L.; Geronikaki, A.; Catania, V.; Schillaci, D.; Gallo, G.; Gitsos, I. Enzymatic Synthesis and Antimicrobial Activity of Oligomer Analogues of Medicinal Biopolymers from Comfrey and Other Species of the Boraginaceae Family. *Pharmaceutics* 2022, 14, 115. [CrossRef] [PubMed]

5. Gomes, P.; Quiro-Querello, L.; Muribecea, A.; Reis, J.; Pamplona, S.; Lima, A.H.; Trindade, M.; Silva, C.; Souza, J.N.S.; Boutin, J.A.; et al. Constituents of *Chamaecrista diphylla* (L.) Greene Leaves with Potent Antioxidant Capacity: A Feature-Based Molecular Network Dereplication Approach. *Pharmaceutics* 2021, 13, 681. [CrossRef]

6. Cotabarren, J.; Ozon, B.; Claver, S.; Garcia-Pardo, J.; Obregon, W.D. Purification and Identification of Novel Antioxidant Peptides Isolated from *Geoffroea decocticans* Seeds with Anticoagulant Activity. *Pharmaceutics* 2022, 13, 1153. [CrossRef] [PubMed]

7. Lee, D.; Alishir, A.; Jang, T.S.; Kim, K.H. Identification of Bioactive Natural Product from the Stems and Stem Barks of *Cornus waltheri*: Benzyl Salicylate Shows Potential Anti-Inflammatory Activity in Lipopolysaccharide-Stimulated RAW 264.7 Macrophages. *Pharmaceutics* 2021, 13, 443. [CrossRef]

8. Tavares, L.A.; Rezende, A.A.; Santos, J.L.; Estevam, C.S.; Silva, A.M.O.; Schneider, J.K.; Cunha, J.L.S.; Droppa-Almeida, D.; Correia-Neto, I.J.; Cardoso, J.C.; et al. *Cymbopogon winterianus* Essential Oil Attenuates Bleomycin-Induced Pulmonary Fibrosis in a Murine Model. *Pharmaceutics* 2021, 13, 679. [CrossRef]

9. Abdalla, M.A.; Li, F.; Wenzel-Storjohann, A.; Suliman, S.; Tasdemir, D.; Mühling, K.H. Comparative Metabolite Profile, Biological Activity and Overall Quality of Three Lettuce (*Lactuca sativa* L., *Asteraceae*) Cultivars in Response to Sulfur Nutrition. *Pharmaceutics* 2021, 13, 713. [CrossRef]

10. Nonpanya, N.; Sanookpan, K.; Sriratanasak, N.; Vinayawanuattikun, C.; Wichadakul, D.; Sritularak, B.; Chanvorachote, P. Artocarpin Targets Focal Adhesion Kinase-Dependent Epithelial to Mesenchymal Transition and Suppresses Migratory-Associated Integrins in Lung Cancer Cells. *Pharmaceutics* 2021, 13, 554. [CrossRef]

11. Kis, B.; Pavel, I.Z.; Haidu, D.; Stefănuț, M.N.; Diaconeasa, Z.; Moačă, E.-A.; Dehelean, C.A.; Sipos, S.; Ivan, A.; Danciu, C. Inorganic Element Determination of *Hainanopsis* nigra L. Buds and In Vitro Anti proliferative and Pro-Apoptotic Evaluation on A549 Human Lung Cancer Cell Line. *Pharmaceutics* 2022, 13, 986. [CrossRef] [PubMed]

12. Kim, M.Y.; Lee, H.; Ji, S.Y.; Kim, S.Y.; Hwangbo, H.; Park, S.-H.; Kim, G.-Y.; Park, C.; Leem, S.-H.; Hong, S.H.; et al. Induction of Apoptosis by Isoantolactone in Human Hepatocellular Carcinoma Hep3B Cells through Activation of the ROS-Dependent JNK Signaling Pathway. *Pharmaceutics* 2021, 13, 115. [CrossRef] [PubMed]

13. Vildanova, M.; Vishnyakova, P.; Saidova, A.; Konduktorova, V.; Onishchenko, G.; Smirnova, E. Gibberellic Acid Initiates ER Stress and Activation of Differentiation in Cultured Human Immortalized Keratinocytes HaCaT and Epidermoid Carcinoma Cells A431. *Pharmaceutics* 2021, 13, 1813. [CrossRef]

14. Vasas, A.; Laier, I.; Küsz, N.; Király, S.B.; Kovács, T.; Körtvélyesi, A.; Bózsi, N.; Nagy, N.; Schelz, Z.; Zupkó, I.; et al. Isolation, Structure Determination of Sesquiterpenes from Neuraolina lobata and Their Anti proliferative, Cell Cycle Arrest-Inducing and Anti-Invasive Properties against Human Cervical Tumor Cells. *Pharmaceutics* 2021, 13, 2088. [CrossRef] [PubMed]

15. Kello, M.; Kuruc, T.; Petrova, K.; Goga, M.; Michalova, Z.; Coma, M.; Rucova, D.; Mojzis, J. Pro-Apoptotic Potential of *Pseudovernia furfuracea* (L.) Zopf Extract and Isolated Physodic Acid in Acute Lymphoblastic Leukemia Model In Vitro. *Pharmaceutics* 2021, 13, 2173. [CrossRef]

16. Wikán, N.; Hankittichai, P.; Thaklaewphan, P.; Potikanond, S.; Nimlamool, W. Oxyresveratrol Inhibits TNF-α-Stimulated Cell Proliferation in Human Immortalized Keratinocytes (HaCaT) by Suppressing AKT Activation. *Pharmaceutics* 2022, 14, 63. [CrossRef]

17. Chen, G.-R.; Chang, M.-L.; Chang, S.-T.; Ho, Y.-T.; Chang, H.-T. Cytotoxicity and Apoptosis Induction of 6,7-Dehydrooroleane from *Taiwania cryptomerioides* Bark via Antioxidant and Epithelial Inactivation in Hepatocellular Carcinoma Cells. *Pharmaceutics* 2022, 14, 351. [CrossRef]
18. Chung, K.-S.; Yoo, C.-B.; Lee, J.-H.; Lee, H.-H.; Park, S.-E.; Han, H.-S.; Lee, S.-Y.; Kwon, B.-M.; Choi, J.-H.; Lee, K.-T. Regulation of ROS-Dependent JNK Pathway by 2′-Hydroxycinnamaldehyde Inducing Apoptosis in Human Promyelocytic HL-60 Leukemia Cells. *Pharmaceutics* 2021, 13, 1794. [CrossRef] 

19. Huang, C.-Y.; Liu, I.-H.; Huang, X.-Z.; Chen, H.-J.; Chang, S.-T.; Chang, M.-L.; Ho, Y.-T.; Chang, H.-T. Antimelanogenesis Effects of Leaf Extract and Phytochemicals from Ceylon Olive (Elaeocarpus serratus) in Zebrafish Model. *Pharmaceutics* 2021, 13, 1059. [CrossRef] 

20. Mattos, E.B.d.A.; Pereira, P.R.; Mérida, L.A.D.; Corrêa, A.C.N.T.F.; Freire, M.P.V.; Paschoalin, G.A.P.B.; Pinho, M.d.F.B.; Vericimo, M.A. Taro Lectin Can Act as a Cytokine-Mimetic Compound, Stimulating Myeloid and T Lymphocyte Lineages and Protecting Progenitors in Murine Bone Marrow. *Pharmaceutics* 2021, 13, 350. [CrossRef] 

21. Lee, D.; Kim, Y.-M.; Chin, Y.-W.; Kang, K.S. Schisandrol A Exhibits Estrogenic Activity via Estrogen Receptor α-Dependent Signaling Pathway in Estrogen Receptor-Positive Breast Cancer Cells. *Pharmaceutics* 2021, 13, 1082. [CrossRef] [PubMed] 

22. Caroleo, M.C.; Plastina, P.; Fazio, A.; La Torre, C.; Manetti, F.; Cione, E. Olive Oil Lipophenols Induce Insulin Secretion in 832/13 β-Cell Models. *Pharmaceutics* 2021, 13, 1085. [CrossRef] 

23. Lim, S.H.; Yu, J.S.; Lee, H.S.; Choi, C.-I.; Kim, K.H. Antidiabetic Flavonoids from Fruits of Morus alba Promoting Insulin-Stimulated Glucose Uptake via Akt and AMP-Activated Protein Kinase Activation in 3T3-L1 Adipocytes. *Pharmaceutics* 2021, 13, 526. [CrossRef] [PubMed] 

24. Neganova, M.; Aleksandrova, Y.; Suslov, E.; Mozhaïtsev, E.; Munkuev, A.; Sukocheva, O.; Volcho, K.; et al. Novel Multitarget Hydroxamic Acids with a Natural Origin CAP Group against Alzheimer’s Disease: Synthesis, Docking and Biological Evaluation. *Pharmaceutics* 2021, 13, 1893. [CrossRef] 

25. Monchaux De Oliveira, C.; De Smedt-Peyrusse, V.; Moreau, J.; Vancassel, S.; Capuron, L.; Pourtau, L.; Castanon, N. Prevention of Stress-Induced Depressive-like Behavior by Saffron Extract Is Associated with Modulation of Kynurenine Pathway and Monoamine Neurotransmission. *Pharmaceutics* 2021, 13, 2155. [CrossRef] [PubMed] 

26. Landucci, E.; Bonomolo, F.; De Stefani, C.; Mazzantini, C.; Pellegrini-Giampietro, D.E.; Bilia, A.R.; Bergonzi, M.C. Preparation of Liposomal Formulations for Ocular Delivery of Thymoquinone: In Vitro Evaluation in HCEC-2 e HConEC Cells. *Pharmaceutics* 2021, 13, 2093. [CrossRef] 

27. Magalhães, B.Q.; Machado, F.P.; Sanches, P.S.; Lima, B.; Falcão, D.Q.; von Ranke, N.; Bello, M.L.; Rodrigues, C.R.; Santos, M.G.; Rocha, L.; et al. Eugenia sulcata (Myrtaceae) Nanoemulsion Enhances the Inhibitory Activity of the Essential Oil on P2X7R and Inflammatory Response In Vivo. *Pharmaceutics* 2022, 14, 911. [CrossRef] [PubMed] 

28. Batista, J.V.C.; Matos, A.P.; Oliveria, A.P.; Ricci Júnior, E.; Freitas, Z.M.; Oliveira, C.A.; Toma, H.K.; Capella, M.A.M.; Rocha, L.M.; Weissenstein, U.; et al. Thermoresponsive Hydrogel Containing Vilbum Extract for Topic and Transdermal Use: Development, Stability and Cytotoxicity Activity. *Pharmaceutics* 2022, 14, 37. [CrossRef] 

29. Paczkowska-Walentowska, M.; Szymańska, E.; Winnicka, K.; Szwajgier, D.; Baranowska-Wójcik, E.; Ruchała, M.A.; Simon, M.; Cielecka-Piontek, J. Cyclodextrin as Functional Carrier in Development of Mucoadhesive Tablets Containing Polygonum cuspidati Extract with Potential for Dental Applications. *Pharmaceutics* 2021, 13, 1916. [CrossRef] [PubMed] 

30. Kobryń, J.; Dalek, J.; Musiał, W. The Influence of Selected Factors on the Aqueous Cryptotanshinone Solubility. *Pharmaceutics* 2022, 13, 992. [CrossRef] [PubMed] 

31. Lupasescu, A.-V.; Iavorschi, M.; Covasa, M. The Use of Bioactive Compounds in Hyperglycemia- and Amyloid Fibrils-Induced Toxicity in Type 2 Diabetes and Alzheimer’s Disease. *Pharmaceutics* 2022, 14, 235. [CrossRef] [PubMed] 

32. Filippiuc, L.E.; Ababei, D.C.; Alexà-Stratulat, T.; Pricop, C.V.; Bild, V.; Stefanescu, R.; Stanciu, G.D.; Tamba, B.-I. Major Phyto-cannabinoids and Their Related Compounds: Should We Only Search for Drugs That Act on Cannabinoid Receptors? *Pharmaceutics* 2021, 13, 1823. [CrossRef] [PubMed] 

33. Manganyi, M.C.; Tlatsana, G.S.; Mokoroane, G.T.; Senna, K.P.; Mohaswa, J.F.; Ntseyagae, K.; Fri, J.; Ateba, C.N. Bulbous Plants Drimia: “A Thin Line between Poisonous and Healing Compounds” with Biological Activities. *Pharmaceutics* 2021, 13, 1385. [CrossRef] [PubMed]