Commentary

Exploring Innovations in Secondary Metabolites and Their Effects on Pain, Inflammation and Metabolic Syndrome

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Secondary metabolites, once considered non-essential by-products of plant and microbial metabolism, have emerged as potent bioactive molecules with tremendous therapeutic promise. Recent advances in biotechnology, omics technologies, and natural product chemistry have enabled the identification and engineering of these molecules at an accelerated pace, highlighting their potential to modulate complex disease mechanisms. This editorial discusses novel breakthroughs in secondary metabolites, focusing on their applications in pain modulation, anti-inflammation, and metabolic regulation. Through exemplary examples, we emphasize the translational potential of these natural products and underline the necessity of an interdisciplinary strategy to surmount current bottlenecks in clinical translation.

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Introduction

The three main kingdoms of life with highly evolved secondary metabolisms are bacteria, fungi, and plants. So far, around 500,000 secondary metabolites—also known as natural products—have been identified. Of these, roughly 100,000 come from animals, 350,000 from plants, and 70,000 from microorganisms.[1] Secondary (specialized) metabolites, which mediate plant-environment interactions, are increasingly valued as multifunctional molecules that operate not only in plant defense but also as potent regulators of growth, development, and adaptation.[2]

Effective treatments for cancer, malaria, bacterial and fungal infections, neurological and cardiovascular diseases, and autoimmune disorders have all been developed using natural products, which remain among the most significant therapeutic agents and lead compounds in medicine.[1] Secondary metabolites, particularly those derived from plants, such as proanthocyanidins, terpenes, stilbenes, and alkaloid analogues like metformin, have been demonstrated in recent research to possess strong neuromodulatory, anti-inflammatory, and analgesic effects across various pain models, including diabetic neuropathy, bone cancer, orofacial pain, and neuroinflammation. Numerous biochemical pathways, including TRPV1, ASIC3, PI3K/Akt/mTOR, NF-κB, and p38-MAPK, are influenced by these natural compounds, suggesting their potential as valuable alternatives or supplements to traditional pharmaceutical and neurostimulation-based pain management treatments.[3]

Recent progress in metabolic engineering, systems biology, and synthetic biology now enables the engineering of microorganisms to produce foreign chemicals in ways once impractical. Showcasing how omics-guided metabolic rewiring allows supply chain stabilisation and scalable production of complex plant-derived therapeutics, Artemisinin, a secondary metabolite sesquiterpene lactone naturally produced by Artemisia annua, was industrially synthesised through biosynthetic engineering with Saccharomyces cerevisiae.[4]

The prediction of biosynthetic gene clusters directly from genome sequences marks a recent advancement in bioinformatics and genetics. This shift has revolutionized

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the exploration of fungal secondary metabolites, moving the emphasis from empirical screening to a more genome-informed, predictive approach. These discoveries uncovered a wealth of previously undiscovered or obscure gene clusters that hold unparalleled promise for investigating novel bioactive substances and gaining access to the chemical diversity of fungi, especially filamentous Ascomycota and Basidiomycota.[1]

Curcumin, a polyphenolic secondary metabolite derived from Curcuma longa, is renowned for its anti-inflammatory, anti-cancer, anti-microbial, and antioxidant effects through the regulation of multiple cellular pathways. Although it has low intrinsic bioavailability, recent advancements like the co-administration of piperine have significantly improved its absorption, facilitating its widespread application in nutrition and medicine, and cosmetics. Also, curcumin has demonstrated exceptional promise in treating metabolic syndrome, where it positively influences oxidative stress, lipid metabolism, insulin sensitivity, and inflammatory cytokine levels.[5]

Continuous research and innovation are required to maximize the therapeutic benefits of secondary metabolites for multifactorial conditions like pain, inflammation, and metabolic syndrome. Transdisciplinary approaches combining systems biology, pharmacology, and biotechnology are crucial for addressing present and upcoming clinical translation issues, as the treatment paradigm acknowledges natural product-based medications.

Conclusion

Secondary metabolites, often plant constituents or natural chemicals, significantly influence human pharmacology and toxicity. Most secondary metabolites interact directly with receptors, cell membranes, and nucleic acids, exhibiting a wide range of therapeutic activities. They provide a vast, unexplored therapeutic arsenal as the global burden of chronic diseases, including metabolic syndrome, neuroinflammation, and refractory pain, continues to take a severe toll. However, multidisciplinary collaboration among natural product chemistry, pharmacokinetics, molecular biology, and translational medicine will be essential for integrating them into effective clinical practice. Investing in integrated strategies that include high-throughput screening, bioinformatics-based target selection, and innovative delivery technologies is crucial for the future. Such measures will be vital in unlocking the full therapeutic potential of secondary metabolites and ensuring they deliver safe, effective, and affordable treatments for modern medicine.

Conflict of Interests

The authors declare no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Consent for Publication

All authors have approved the manuscript and consent to its publication.

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