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Editorial overview: Microbial and plant enzymes in sustainable chemistry and pharmacy

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This review comes from a themed issue on **Microbial and Plant Enzymes in Sustainable Chemistry and Pharmacy**

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Nicolas Papon studied biology and biochemistry at the University of Tours (France). After a PhD in plant biology (2000–2003), he was first recruited as a lecturer in botanics and mycology at the Faculty of Pharmacy in Paris. In 2008, he then moved as an assistant professor in biotechnology at the Faculty of Pharmacy, University of Tours. He finally moved to the University of Angers in 2015 and was appointed a professor in parasitology, medical mycology, and health biotechnologies. He is currently working as an assistant director of the Host–Pathogen Interactions Study Group, University Hospital of Angers.

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Vincent Courdavault initially studied protein prenylation in plants during his PhD studies. Since 2006, he has held a faculty position at the University of Tours where he is currently an associate professor. His current research involves the elucidation and bioengineering of natural product synthesis with a particular focus on monoterpene indole alkaloids synthesized in Apocynaceae. He is managing several projects related to natural product synthesis and valorization.

Enzymes represent an outsize series of protein catalysts produced by near to all living organisms. Beyond acting in many important metabolic pathways or regulating a broad range of physiological processes in both prokaryotes and eukaryotes, enzymes are now also unavoidable for human activity including industry but also health and environmental sciences. While being currently mainly used in a productive view, enzymes also offer new opportunities toward the development of sustainable solutions to synthesize/recycle/valorize in an eco-friendly manner. This themed issue published in *Current Opinion in Green and Sustainable Chemistry* presents a collection of perspective reviews by research groups from Europe, America, and Asia discussing the latest advances and future directions concerning the uses of microbial and plant enzymes in sustainable chemistry and pharmacy.

Many hundreds billion tons of agro-industrial wastes accumulate each year on Earth. There is obviously an urgent need in developing new valorization strategies of these wastes that could represent an inexhaustible source of valuable products but also energy, according to the 5R concept (reduce, reuse, recycle, recovery, and restore). **In this regard, the first topic of this special issue throws light on the importance of microbial enzymes in sustainable chemistry and pharmacy through a series of five enlightening articles.**

First, Luisa Fernanda Rojas, Paola Zapata, and Laura Ruiz-Tirado critically review the most recent studies on agro-industrial waste enzymes and their perspectives in circular economy. Co-workers notably detail how the integration of enzymatic technologies with the classic processes of physicochemical transformation of agro-industrial waste will continue to be a key step to increase the supply of non-energy products. Recent advances in nanotechnology, metabolic engineering, and multi-omics platforms may also help in optimizing the valorization of both biomass and microbial communities associated with the different sources of waste, enhancing the resources of developing countries.

In the same vein, Marie-Noëlle Rosso, Jean-Guy Berrin, and Anne Lomascolo provide an overview of the most recent findings in the hydrolytic and oxidative systems fungi use for the degradation of recalcitrant

plant polymers. Authors compile recent promising successes in applying fungal enzymes or fungal fermentations on plant wastes while discussing the forthcoming developments that could reinforce fungal biotechnology entering a variety of industrial applications.

In order to use lignocellulosic biomass for industrial fermentation, efficient enzyme hydrolysis is essential. In such a perspective, attaching enzymes to the surface of microorganisms offers a clear advantage compared to conventional processes, as it allows the multiple reuses in different batches of the displayed enzymes. In this respect, the review by Takahiro Bamba, Gregory Guirimand, Akihiko Kondo, and Tomohisa Hasunuma highlights recent advances in the applications of cell surface engineering for efficient utilization and valorization of lignocellulosic materials.

This topic is finally filled out with a couple of reviews focusing on specific classes of fungal proteins. First, Huei-Mien Ke and Isheng Jason Tsai critically consider the recent progress and future perspectives in fungal bioluminescence. Beyond covering the current understanding in the diversity and evolution of these light-emitting pathways involving critical enzymes referred to as luciferases, authors also discuss how it would be possible in a near future to design and use this pathway for specific purposes, even reconstructing self-sustained glowing plants that illuminate city streets may one day be possible.

The second review by Camille Sayou and Jérôme Govin examines and emphasizes the discussion on the inhibition of BET bromodomains for developing new treatments for fighting human pathogenic fungi. While targeting these essential proteins recently emerged as a potentially valuable antifungal strategy, coworkers remind us that there is still a long way to go before clinically transferable compounds become available. Notably, active research is urgently needed to clarify the molecular basis of BET inhibition and its physiological consequences on fungi in relation to infection.

Besides microbial enzymes, we dedicated the second main topic of this themed issue to the ever-growing role of plant enzymes in sustainable chemistry and pharmacy. More specifically, the following series of outstanding articles provide a global overview of applications on plant enzymes involved in specialized metabolism pathways (also termed "secondary metabolism pathways") for the development of new cell factories aiming at revolutionizing the supply of plants drugs, including for instance anticancer and antimicrobial molecules.

As observed in bacteria and fungi, enzyme-encoding genes involved in the synthesis of these valuable compounds are sometimes neighbors on the genome and therefore constitute metabolic gene clusters (MCGs). In this respect, Guy Polturak, Zhenhua Liu, and Anne Osbourn present in this issue new and emerging concepts in the evolution and function of plant MGCs. More specifically, the authors summarize some key advances in the field of plant MGCs, including the diversity of plant specialized metabolism that they encode, the metabolic networks they form, and new insights into cluster evolution and regulation.

For many decades, the manufacturing of plant-derived pharmaceuticals using extraction from natural resources or chemical synthesis poses recurrent challenges. In such a perspective, the production of plant drugs in engineered microbes can nowadays offer an attractive alternative as these processes reduce the use of natural plant resources and instead rely on renewable feedstocks as raw materials. In practice, this consists in heterologously expressing plant enzymes in a bacterial of yeast cell for allowing the microbe to sustainably produce the desired plant product. This theme is first nicely introduced by David Romero-Suarez, Jay D. Keasling, and Michael K. Jensen compiling emerging metabolic engineering strategies aiming at supplying plant natural drugs by yeast cell factories.

Since the pioneering proof of concept provided by the microbial production of an artemisinin (a main antimalarial natural product originally extracted from wormwood) precursor, recent works have demonstrated the feasibility of microbial production platforms for several families of plant-derived drugs. In line with this first article, Michael E. Pyne and Vincent J. J. Martin summarize such recent advancement concerning a specific family of plant metabolites, namely tetrahydroisoquinoline (THIQ). THIQ indeed includes several natural, synthetic, and semi-synthetic drugs approved for the treatment of cancer, pain, gout, and various neurodegenerative diseases. In this excellent review, co-authors outline new advancements in the production of THIQ products in microbial cell factories and discuss achievements in THIQ enzyme discovery, as well as ongoing efforts to reconstruct newly discovered pathways and engineer novel THIQ synthesis routes in microbial systems.

Even though the development of microbial strains with laboratory scale titers of production, high-scale heterologous production of plant drugs encounters a broad range of obstacles due to the complexity of plant metabolic pathways. Thus, much work remains to be performed before reaching industrial-scale production strains that can be used for commercialization and some improvement paths have recently emerged to this aim. For instance, we know now that the spatial organization of some metabolic pathways, typically across multiple cellular compartments, seriously encumbers engineering success. In this regards, Ana Cristina Jaramillo-Madrid, Elia Lacchini, and Alain Goossens discuss the

recent advances in endoplasmic reticulum, peroxisome, and other organellar engineering and illustrate how this is being applied to increase terpene pathway performances in plants and yeasts. In addition, some recent breakthroughs teach us that specialized transporters could present potent novel tools to connect cellular compartments. This feature is specifically addressed in the article by Zeinu Mussa Belew, Michal Poborsky, Hussam Hassan Nour-Eldin, and Barbara Ann Halkier. Authors provide particular emphasis on how transport engineering in microbial cell factories producing plant specialized metabolites can overcome main hurdles such as premature pathway termination due to secretion of intermediates and feedback inhibition due to inefficient export of final products. Finally, Helena H. Chubatsu Nunes, Trinh-Don Nguyen, and Thu-Thuy T. Dang how plant enzymes enrich our toolbox for engineering purpose from harnessing the potential of stand-alone enzymes up to "one-pot" biosynthetic reactions based on attractive cell-free approaches.

We hope this special issue provides both inspiration and a driver for further research in the field of microbial and plant enzymes in sustainable chemistry and pharmacy. Such developments, at their scales, could indeed constitute an invaluable chance to further achieve a better and more sustainable future for all.

Declaration of competing interest

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

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