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Opinion: The accustomed inconsistency in biochemical ecology – Enhanced knowledge of the evolution and function of natural products frequently implies teleological misinterpretations

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Summary

Secondary plant products are the basis for complex interactions between plants and their environment. By protecting plants against pathogens and herbivores or by attracting potential pollinators, they accomplish various and distinct ecological functions. The enormous diversity of these natural compounds is the result of evolutionary processes that have been driven by the selection of corresponding advantageous properties. Unfortunately, when discussing this context, we frequently formulate statements such as "Plants have acquired the ability to synthesize secondary plant products in order to…" without realizing that such assertions contradict the Darwinian principles of evolution and thus represent the Lamarckian view of a teleological evolution. The primary reason for these unconscious misapprehensions seems to be the ambiguous usage of the term "biological function", whose denotation frequently includes an intention or a special purpose. In this treatise, the related associations and conclusions are outlined and depicted.

Key words: biological function; ecological biochemistry; evolution; natural products; secondary plant products.

Preamble

Professor Reinhard Lieberei was one of the leading scientists in the field of applied botany. Apart from his great achievements in this area, he was also deeply committed to ecological biochemistry. Based on a holistic way of thinking combined with comprehensive knowledge of plant physiological coherences, he developed a distinguished understanding of ecological biochemistry. His related statements were sophisticated and descriptive, and he omitted misleading simplifications. He opened new doors, developing the basis for quite novel comprehensive approaches, particularly in the field of applied botany. The broad spectrum of Lieberei's important achievements in this area and his scientific impact become obvious when reading the various articles by his scientific scholars and companions, compiled and displayed in this special section.

For Lieberei and his scientific self-conception, and in particular for his way of understanding biological processes, Darwinian principles had always been essential and inevitable – they came first and foremost also in the field of ecological biochemistry. Indeed, we all are convinced to have internalized these general principles. However – especially when addressing biochemical ecology – many scientists seem to forget or even ignore them and frequently drift into Lamarckian argumentation and teleological conceptions. I still have strong memories of many divisive and vivid discussions with numerous renowned colleagues in which Lieberei tried to pinpoint the respective inconsistencies. Together with professor Böle Biehl, the academic mentor of Lieberei, who also passed away in 2019, we discussed these misapprehensions extensively and pervasively many times. Inspired by these experiences, in this treatise I outline how our increased understanding of biochemical ecology and the metabolism of secondary plant products frequently generates inaccurate statements concerning their evolution and function.

Secondary metabolism, its evolution and teleological misinterpretations

In recent decades tremendous progress in the understanding of secondary metabolism has been achieved. Moreover, many novel insights into ecological biochemistry have been generated, verifying that secondary plant products reveal important functions within the complex interactions between plants and their environment (current comprehensive reviews have been compiled, such as by Mérillon and Ramawat, 2020). Today, there is no doubt that plants are protected by accumulating toxic, bitter or pungent tasting substances such as alkaloids or phenolics, which effectively repel potential herbivores (for review see: Hartmann, 2007; Zenk and Juenger, 2007). Similarly, pathogens are fended off by the synthesis of various phytoalexins or by toxic phytoanticipins. Furthermore, we know that pollinators are attracted by pigments or scents of flowers. Based on the tremendous progression of molecular and cell biology, the complex biosynthesis of many natural products has been comprehensively elucidated, and the involved genes have been identified and characterized (related reviews are compiled by Wink, 2010). Finally, in many cases, the underlying regulation processes have been explored and unveiled (e.g. Zhang and Memelink, 2009; Del Carpio et al., 2014), and we are aware that the enormous diversity of natural products is the result of evolutionary processes driven by the selection of advantageous properties (e.g. Hartmann, 2007; Firn and Jones, 2009). In addition, extensive studies have indicated that genes involved in secondary metabolism originated by duplication of those responsible for primary metabolism with successive diversification (Ober, 2010; Moghe and Last, 2015).

All in all, our general understanding of secondary metabolism is profound, and the major relationships are quite clear. Unfortunately, this comprehensive knowledge in combination with deep insights into metabolism often generates an oversimplified perception of the entire issue. Many discussions of the topic include not only inaccurate but even erroneous statements, in particular when accounting for the relationships between function and evolution of natural products. In this context, one of the common assertions is: "Plants have acquired the ability to produce and accumulate numerous secondary plant products in order to protect themselves against herbivores". Indeed, when considering the numerous excellent examples of plant-herbivore-interactions in the literature and the tremendous approaches in modern chemical ecology, superficially, this statement seems to be correct. However, when carefully scrutinising the meaning, it becomes obvious that the phrase "in order to protect" is inappropriate: this statement implies that the evolutionary processes which have created and established secondary metabolism are directed to a specific goal and to fulfil a certain purpose. This, in turn, would imply that *evolution is target-oriented*. Well, in general, we all are aware that evolution does not follow Lamarck's theory, which depicts a teleological, goal-oriented process. In this regard, we know that giraffes did not develop longer necks *in order* to feed on treetops. Unfortunately, when referring to secondary plant products, this basic nexus is ignored, and even honourable and knowledgeable experts are trapped by this flaw when allegorising or exemplifying this topic. Accordingly, in many releases – especially in those dealing with biochemical, molecular biological or molecular genetic topics – the corresponding objections seem to be forgotten. Obviously, we are so impressed by the tremendous progress we have made and the details we have elucidated that the basic scientific fundamentals are neglected. Teleological considerations, and the related deductions, are not reliable and are consequently unscientific.

In principle, the relationship between function and evolution of natural products seems to be very simple. Caused by mistakes in gene replication or odd recombinations in crossover, mutations occur frequently, which might be accompanied by duplication of genetic material. As the genuine function of the duplicated gene, or the related enzyme, is maintained by the original gene, there is no massive selection power to rapidly knock out the duplicate. Accordingly, due to further mutations, successive diversification might take place. Indeed, when these processes result in properties that create a disadvantage for the organism, they will be selected out of the gene pool. By contrast, when the mutations create repercussions that enhance fitness (e.g., by increased pollination efficiency, or better protection against herbivores), this organism will be favoured. In this manner, evolution of the large diversity of secondary plant products can be explained.

In addition, as a further significant issue with respect to the evolution of secondary metabolism, the presence of promiscuous enzymes has to be considered. Indeed, originally, it was postulated that the enzymes involved in secondary metabolism were highly specific (e.g., Hartmann, 1996; Wink, 1997). However, we have learned that substrate specificity of enzymes is far lower than initially assumed (e.g., Atkins, 2015), and various enzymes, denoted as moonlighting proteins, are known to be responsible for the catalysis of different metabolic reactions (Jeffery, 1999). In consequence, promiscuous enzymes are also thought to serve as evolutionary starting points with respect to secondary metabolism (Khersonsky and Tawfik, 2010). Nonetheless, with respect to the contribution of promiscuous enzymes in the evolution of secondary metabolism, we have to be aware that evolution is not target oriented but represents the outcome of a selective process (Kreis and Munkert, 2019).

With respect to the evolution of secondary metabolism, another aspect which is frequently is misjudged is the tall story of "cost-benefit considerations". In this context many related publications have stated: "with respect to secondary metabolism the cost versus benefits have to be balanced". Indeed, due to our recurring experience in daily life, we all have internalised that energy conservation represents one of the most important issues in our subsistence. Accordingly, it seems reasonable at first glance to transfer such importance also into plant biology. However, in this context we have to consider that plants – in contrast to heterotrophic organisms – face less of a challenge in covering their energy requirements. Indeed, plants generally absorb much more energy than required for photosynthetic CO_2 fixation (Wilhelm and Selmar, 2011). As a result, plants have to dissipate a tremendous oversupply of energy in order to avoid massive damage by oxygen radicals, resulting from overreduction of the electron transport chain, which would destroy the leaves (Reddy et al., 2004; Szabó et al., 2005). Apart from the various classical mechanisms for effective energy dissipation (i.e., non-photochemical quenching, photorespiration, or xanthophyll cycle), especially under stress conditions, the synthesis of highly reduced compounds also contributes to effective energy dissipation (Selmar and Kleinwächter, 2013a). In this context the massive emission of isoprene represents one of the most intriguing examples (e.g. Fall 1999; Sharkey and Yeh, 2001). Thus, the synthesis of highly reduced secondary plant products does not correspond to a "cost of energy" but contributes to the unequivocally required energy dissipation (Selmar and Kleinwächter, 2013b; Kleinwächter and Selmar, 2015; Yahyazadeh et al., 2018). This vividly displays that – even without a distinct ecological function – the synthesis of natural products involves an evolutionarily relevant advantage, facilitating the evolutionary generation and establishment of ecologically relevant natural products.

Biological function – a term which frequently generates misapprehensions

The primary reason for the unintended teleological statements regarding the ecological significance of secondary metabolism discussed above is certainly the ambiguity of the term "function" and the related discrepancy between its basic, inherent meaning and its extended usage (Selmar, 2009). In natural sciences, a function *in stricto senso* corresponds either to a mathematic relationship, for example $y = f(x)$, or in an extended sense, it describes a link of a causal sequence in which one parameter, based on a set of stipulations, determines another parameter. Accordingly, the term "function" describes a response to a certain event or the related consequence without entailing any purpose or intention. In contrast, in our daily life the term "function" is applied teleologically, and routinely it includes a *significance or relevance*, implying that a function *per se* accomplishes a certain purpose (Selmar, 2009). In this sense, we are accustomed to tools having a distinct function and implementing a specific purpose. As result, the ambiguous meaning of "function" has been adopted and internalized in the biological sciences, generating the equivocalities mentioned.

Based on approved experimental techniques, plant metabolism has been extensively analysed, and the processes involved have been comprehensively investigated. Although in many cases only a limited section of a certain area has been elucidated, based on reliable results and appropriate causal chains, we can use understanding of single parts of the system to comprehend the entire organism. As we have internalised conceptualisation of the operation of mechanical devises by identifying the various functional elements and tools (e.g. clutch, conveyor, energy supplier), we have tried to explain the various metabolic processes and even the entire metabolism analogously. Thus, we attribute and assign a "particular function" to a certain metabolic process. Although an extended use of the term "function" in the sense of "purpose" virtually contradicts its valid scientific definition by neglecting the sound principle of causality, related statements and deductions are suitable – if they are based on an extended definition including the intent of a function. However, the inaccuracy and the unscientific actions begin when these teleological reflections are expanded with respect to evolutionary considerations in statements like: "…in the course of evolution a certain metabolic process was created *in order to* fulfil certain functions". This, unfortunately, is particularly true for secondary metabolism, since it is frequently stated that "…natural products were generated in the course of evolution *in order to* protect the plants".

In modern biology such ambiguity should be avoided by relying on the Darwinian principles of mutation and selection. We always are on a solid scientific basis when – based on reliable experimental methods and by employing sound causal chains of established evidence – we deduce that in phylogenetic history, selection of certain modified reaction patterns has occurred and organisms adapted to special environmental conditions and – in the sense of the meaning outlined above – a certain function is thereby established. But we should be aware that such a statement is not equivalent to the teleological assertion that mutation and selection automatically generate a certain purposeful mechanism, fulfilling a predetermined goal. Indeed, such knotty explanation can be quite problematic when explaining the issue to a broad community. Nonetheless, we should avoid teleological statements such as "…evolved in order to protect…" and emphasize scientifically sound deductions based on Darwinian principles. In this context, I remember quite well the outcome of a long and fruitful discussion with Reinhard Lieberei, who stated appropriately: "In the course of evolution, plants have acquired the ability to synthesize and accumulate a tremendous diversity of natural products. The presence of these compounds entails selective advantages, e.g. by protecting the plants against herbivores or pathogens or by attracting pollinators. Accordingly, these natural products reveal an essential role in various plant-environmental-interactions by accomplishing vital ecological functions."

Commentary

This discourse is a progression of a disquisition published about ten years ago (SELMAR, 2009). The consistent development of the entire topic was massively expedited by vivid and profound discussions with Reinhard Lieberei.

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