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The modern clinical use of hallucinogens. What can we learn from the natural product research?

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Abstract

Can the emerging field of psychedelic research benefit from natural product research? We believe it can. In this manuscript we delineate certain topics of research with hallucinogens that directly connect with research on natural products in general.

Graphical Abstract

Research around hallucinogenic drugs has increased exponentially since the first years of the 21st century (Hadar et al. 2022). At the time these lines are being written, both psilocybin and MDMA are undergoing Phase-III trials for the treatment of major depressive disorder (MDD) and post-traumatic stress disorder (PTSD), respectively. Remarkably, the innovative mechanisms (including a rapid and sustained neural plasticity as well as profound psychological effects; Vollenweider and Smallridge 2022) and framework (psychedelic-assisted psychotherapies; Gardner et al. 2019) of these treatments are having a major impact in the clinic and in the field of public policy, promoting changes in the regulation of these substances/products (Dos Santos et al. 2021; Smith and Appelbaum 2021).

Despite the promising data on the safety and efficacy of hallucinogenic drugs obtained in randomized and controlled clinical trials (RCT), it should be noted that such trials are still scarce and preliminary, as the field is still emerging, and, thus, findings should be interpreted with caution. In addition, many pitfalls and gaps in the current body of research are increasingly being noted by various authors

(Bradberry et al. 2022; Hayes et al. 2022; McClure-Begle and Roth 2022; Ona et al. 2022{Comment by **Author:** Ona G, Kohek M, Bouso JC. 2022. The illusion of knowledge in the emerging field of psychedelic research. New Ideas Psychol. 67:100967. }; Rossi et al. 2022). Considering all of this, it can be concluded that the field of research concerning hallucinogens requires improved methodologies in order to offer robust evidence to clinicians, patients, and also policy-makers and stakeholders.

Most hallucinogens are, indeed, of a natural origin (psilocybin, active principle of fungi of the *Psilocybe* genre; ayahuasca, a decoction containing the *Banisteriopsis caapi* and *Psychotria viridis* plants; ibogaine, an alkaloid of the *Tabernanthe iboga* shrub; and even ketamine can now be considered a natural product (NP) from the *Pochonia chlamydosporia* fungus; Ferreira et al. 2020). For this reason, we suggest that the well-established research with NPs can offer valuable insights for hallucinogen researchers. Certain relevant topics will be outlined below.

Natural product research is a heterogeneous, long-standing field. Despite advancements in molecular biology and the production of biological drugs, NPs remain one of the main sources for the development of pharmaceuticals (Newman and Cragg 2020). These products are usually highly complex in terms of their chemistry, and, therefore, they may require specific preparations or formulations in order to obtain benefits in a clinical setting. For instance, while in the cases of digoxine or atropine it is necessary to isolate or synthetize these compounds for their clinical use, plants like *Hypericum perforatum* L. and *Artemisia annua* L. display an enhanced therapeutic effect when the whole product is used (Efferth and Koch 2011). In the case of natural hallucinogens, this has barely been explored. With the exception of ayahuasca, the general trend is to use only active principles in research (e.g. psilocybin, ibogaine). This approach has its pros and cons, but it is certainly possible that, for some of these products, the use of complex mixtures rather than isolated molecules would be preferable (Ona et al. 2020; Ona and Bouso 2021). This could be assessed through clinical studies comparing the efficacy of pure psilocybin with extracts of *Psilocybe* mushrooms, for example. In the case of ibogaine, a molecule that poses serious risks due to the prolongation of the QT interval, it would be interesting to assess whether the extracts of *T. iboga* or *Voacanga africana* (some of the plants containing ibogaine), or complex mixtures of iboga alkaloids, have a safer profile, as occurred with the product Quinimax. This commercial product containing cinchona alkaloids prolongs the QT interval to a lesser extent than quinidine alone (Sowunmi et al. 1990).

In relation to the previous point, traditional knowledge has played a central role when researching NPs. The clinical use of hallucinogens, however, does not much resemble their traditional use (starting with the type of product used), and, therefore, it could be improved. Further studies could delve deeper into aspects like the setting and the cultural frameworks within traditional medicine, using these products to identify potentially beneficial synergies.

The current study of hallucinogens hardly benefits from contemporary techniques that are, indeed,

carrying forward the research in NPs. A good example of this are the 'omics.' These techniques offer integrated knowledge through the evaluation of gene expression and the proteome or the metabolome, unraveling molecular signatures predictive of drug response. In this way, using metabolomics specifically, all metabolites contained in a NP can be qualitatively and quantitatively analyzed (Harvey et al. 2015). Only ayahuasca has been tested using these techniques so far (Katchborian-Neto et al. 2020), showing unexpected neuroprotective effects due to synergies among some of its compounds. Other issues that have been highlighted in regards to the limitations of NP research include the difficulty of determining their precise mechanism of action, since complex interactions often occur both within the compounds of the NP and with their biological targets (Bernardini et al. 2018). In that sense, 'omics' and other modern techniques related to network pharmacology (especially relevant are the excellent works describing the mechanisms of multicomponent herbal drugs in the context of traditional Chinese medicine; see for example Liu et al. 2022) are able to unravel these obscurities. The use of hallucinogens in clinical settings would benefit greatly from such insights.

One aspect connected to NP research that has not yet been explored is the possibility of the commercialization of natural hallucinogens that can be widely found in nature. For instance, in the case of cancer treatments, there is a remarkable scarcity of Phase-III RCT with food or dietary supplements from a natural origin that showed promising results in Phase-II RCTs. This might be because manufacturers of those NPs have sufficient data from the Phase-II RCTs to promote and sell their products, as the larger, more expansive Phase-III RCTs make regulatory approval unnecessary (Paller et al. 2016). Accordingly, despite the current large investment in Phase-III RCTs in the case of hallucinogens, there is a possibility that people will prefer to use self-supplied natural hallucinogens after their commercialization approval, instead of the commercial product. The existence of robust networks of underground therapists and practitioners (Inserra 2019; Pilecki et al. 2021; Goldhill 2022), and the possibility of individuals easily accessing most natural hallucinogens (Steinmetz and Kohek 2022) might contribute to a marked decrease in investment return. Notably, this is the case with ketamine and Spravato (esketamine) since, despite the regulatory approval of esketamine, most clinicians prefer to use ketamine due to the much higher cost of esketamine.

In conclusion, there are several topics within contemporary hallucinogen research that connect with the long-standing field of research into NPs. Researchers involved in the former would benefit from applying some of the lessons that have been learned working with NPs in general. The organization of special issues of NP journals focused on hallucinogens, dialogues on platforms like seminars and conferences, and collaborations between authors coming from different disciplines would all contribute to intertwining the two fields.

Disclosure statement

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