Editorial: Improving the data reproducibility and general interest of natural product submissions

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Main text

In modern drug discovery processes, analogues derived from natural products remain a surprisingly successful source of FDA-approved new therapies. Indeed, about one third of new molecules approved in the recent decades are natural compounds or derivatives [1]. These include crucially important immunosuppressant drugs relevant to the scope of this journal, such as sirolimus, cyclosporine, tacrolimus and the antineoplastic taxanes. One key reason for the continued success of natural small molecules may be that the core ring scaffolds of natural compounds, with their complex stereochemistry, are excellent prototypes of pharmacophores that often surpass the structures obtained using combinatorial libraries [1]. Therapeutic peptides/proteins are also of natural origin, but their pharmaceutical applications are generally dependent on specific production technologies that differ from the fractionation of natural extracts (total synthesis for peptides and biotechnological production of recombinant proteins).

In 2006, the Editors of *International Immunopharmacology* introduced guidelines for submitted manuscripts dealing with natural products [2]. In the present discussion, we intend to reaffirm and expand these editorial advices, consistent with the standards of contemporary molecular pharmacology.

1. *International Immunopharmacology* will consider manuscripts dealing with structurally defined and pure chemical compounds. Natural extracts that contain multiple components may be investigated if fractionation and analytic techniques that resolve the

active principle(s) to defined molecule(s) are fully described. These are stepping stones toward the definition of a molecular mode of action and increase the reproducibility and scientific value of the reports. Adjuvant and vaccine research may occasionally deviate from this guideline.

2. Folk medicines are the object of ethnopharmacology; centuries-old traditions may be valid in many cases. If a manuscript intends to elucidate the mechanism of action of a traditional remedy, it must cite proper clinical evidence of the folk remedy efficacy (unfortunately rarely available up to the standards of formal clinical trials) [3]. Then, the study must deal with a pure and defined molecule. Finally, if the remedy is orally administered, authors should address pharmacokinetic considerations such as bioavailability, resistance of the active principle to first-pass hepatic inactivation and effective distribution to target tissues. Evidence of *in vivo* therapeutic efficacy strengthens the priority of such reports.

3. Ideally, the molecular target of studied natural drugs should be known or identified. One particular aspect of this guideline concerns products of vegetal origin because plants commonly contain antioxidants under the form of polyphenolic tannins, flavonoids, etc. In mammalian cells, the number of redox-sensitive signaling pathways is large and they include several relevant to immunity and inflammation (NF-κB, AP-1, Nfr2, cyclooxygenases etc.) [4]. Therefore, corroborating the effect specificity *via* the study of

several pathways is a good experimental practice. The *in vivo* validation of efficacy and tolerability is also useful.

4. Investigated compounds derived from natural sources or recombinant proteins must be endotoxin free to avoid confusion from the signaling of the innate immune system. This is particularly crucial when such a compound is applied to a culture of immune cells or injected *in vivo.* This Special Issue contains a paper expertly dealing with this concern [5]. Analytical methods for endotoxin contamination and steps for its removal should be described.

5. Sufficient controls should be included. The investigated drug should be tested alone (without the experimental pathology) for any effect on the most important outcome parameters. A known positive control drug for the investigated therapeutic effect of a natural compound and a discussion of the possible advantages of the new therapy (e.g., increased efficacy, decreased side effects) should be incorporated.

6. Research involving modern adjuvants and vaccines is encouraged.

7. Manuscripts dealing with cancer immunotherapy are especially invited.

8. Manuscripts dealing with dietary interventions, such as prebiotics and probiotics, are usually not considered.

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