Review of: "On the pros and cons of utilizing crude herbal preparations as opposed to purified active ingredients, with emphasis on the COVID pandemic"

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Potential competing interests: In the past I received consultancy or speakers' fees from Braun, UCB, Sandoz, Abbvie, Zentiva, Teva, Laropharm, CEGEDIM, Angelini, Biessen Pharma, Hofigal, AstraZeneca, and Stada.

„First, a given medication may have numerous possible interactions with other medications, as well as with food and supplements[8]. Second, the metabolism of drugs may vary between different patients[9]. These factors are rarely being taken into account in RCTs. It is generally assumed that the maximal dose that has been tolerated in a clinical trial is suitable for all patients. Yet, often times more is not better."

The fact that a medication has numerous potential interactions and the metabolism may vary greatly inter- and intra-subjects does not imply that consistent dosing is not necessary. Of the contrary, adding an additional source of variability (the herbal product) is expected not to improve the therapy, but rather to complicate it. As for the sentence, "It is generally assumed that the maximal dose that has been tolerated in a clinical trial is suitable for all patients", the authors provide no reference to support it. Moreover, the analysis of many official prescribing information documents in different geopolitical systems will show that the maximum dose is not considered suitable for all patients, and often various ways of adjusting the posology are recommended (whereas in some cases, depending on the PK/PD profile of the active ingredient simpler posology schemes may be recommended).

"Importantly, while most herbal preparations have not been tested in large-scale RCTs, their safety has been assessed for hundreds of years." This is true for some well-known herbal products, but for many it is not, and in this sense it is sufficient, for instance, to consult the herbal monographs reports of the HMPC of the European Medicines Agency.

"Another benefit of using plants, as opposed to medications is that they do not contain excipients, which were thought to be inert substances and have become a significant cause of adverse reactions." The only reference in the support of this statement mentions specifically allergies. However, herbal products can also cause allergies and many foods, including strawberries, nuts, lupins, soy etc could also cause allergies (see, e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10088878/) . Otherwise, the regulatory requirements for conventional medicines do impose inertness on excipients, and cases where such a requirement is not satisfied may result in the prohibition of those excipients (see e.g. the cases of parabens or titanium oxide).

"Indeed, traditional Chinese medicine has been used successfully and has been shown to be safe and effective in small-scale RCTs conducted in China." The problem with this statement is that those small-scale RCTs are affected by at least

small-sample size bias, leaving aside other potential sources of bias. Therefore, the available evidence is of a too low quality to allow an appropriate evaluation.

“Yet, due to the lack of exact dosing and solid scientific proof of efficacy in RCTs, their employment was widely discouraged in many Western countries”. Actually, the only citation supported this statement comes from a paper whose authors are mostly from non-Western countries and apparently with good reason: “The anecdotal use of *Artemisia* spp. extracts for COVID-19 treatment in low-income countries has led to exaggerated and unproven claims of its efficacy in the absence of a scientific basis or results from clinical trials.” Nowhere in that paper do the authors refer to “many Western countries” discouraging the use of the product. They only state that there are “exaggerated and unproven claims of its efficacy in the absence of a scientific basis”. In our view adding a political dimension to a purely scientific question is not in the interest of science.

“It should be taken into account, though, that the traditional treatment approach is not always suitable for statistically based RCTs, which are disease- and not patient-oriented…”. We rather disagree with this statement. RCTs use most often patients as subjects, are based on protocol that contain inclusion and exclusion criteria referring specific to patients, are careful to report adverse effects (and sometimes PROs), are as much focused on patients as on the disease. Of course the protocol imposes standardization to allow interpretation of results, but to claim that RCTs “are disease- and not patient-oriented” does not seem to be a valid statement.

Their findings about the use of Artemisia among the 75 patients are interesting, but it was preferrable to use a more systematic of reporting their finding. Also, while the authors acknowledge that this was not an interventional study, they do not discuss at all the limitations to those observations. It is known that the fatality rate is rather low for COVID-19 (in one estimation, for the non-elderly, as the authors suggest were most of these patients, the fatality rate was 0.095%). Therefore, the fact that no fatality or serious form of the disease was recorded among the small subset of users is not necessarily evidence of efficacy. There may be some effect or may be not. It would have been therefore very useful to provide a clear picture of those patients, with appropriate statistical analyses and acknowledgement of the limitations of this analysis. The paper is therefore useful only as a hypothesis generating paper and, as already indicated by the authors they cited, a properly designed clinical trial should assess the efficacy of such an intervention.