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LETTER TO THE EDITOR

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Phytotherapic compounds against coronaviruses: Possible streams for future research

Dear Editor,

Recently, an epidemic disease outbreak caused by a novel human coronavirus named "SARS-CoV-2" (similar to SARS-CoV and MERS-CoV), first reported in China, has surged worldwide (Li & De Clercq, 2020). No vaccination against SARS-CoV-2 exists to date and available therapeutic options are still limited (Li & De Clercq, 2020). Our aim is to briefly describe the potential help of phytotherapy research in finding new integrative therapeutic options against human coronaviruses, and to provide researchers with some essential hints to be used for planning future studies.

Evidence in support of the activity of medicinal plants (or their extracts) against coronaviruses mostly derives from laboratory studies, whereas clinical data are limited and especially refer to multicomponent herbal preparations used in Traditional Chinese Medicine (TCM) (Liu, Zhang, He, & Li, 2012). In a Cochrane review published in 2012, it was concluded that, although the methodology of included trials was questionable, TCM herbal remedies in addition to Western medicine may help to improve symptoms, quality of life, absorption of pulmonary infiltration, and may decrease the dosage of corticosteroids in patients with SARS (Liu et al., 2012). TCM is highly valued by the Chinese government in their current campaign to contain and eradicate SARS-CoV-2, and from March 1, 2020, a total of 303 ongoing clinical trials aiming to evaluate the efficacy and safety of treatments for Covid-19 patients have been launched in China. Among them, 50 trials (16.5%) are about the use of TCM, including 14 cases (4.6%) which investigate the effect of combined treatment with TCM and Western medicine. In 22 TCM trials (7.3%), the effect of self-made herbal preparations such as Xin Guan-1 Formula, Xin Guan-2 Formula, and QingYi-4 are examined. In another 14 TCM trials (4.6%), commercially available TCM products such as Tan Re Qing injections and Lian Hua Qing Wen capsules are studied (Yang, Islam, Wang, Li, & Chen, 2020), and beneficial effects have been also suggested in two recent reviews about various TCM herbal remedies for SARS coronavirus infections (Luo et al., 2020; Yang et al., 2020). Despite the complexity of TCM formulations, herbs like *Glycyrrhiza glabra* or *Scutellaria baicalensis* were present in more than one tested TCM preparation, and for glycyrrhizin and bacalin (extracted from these herbs) there is in vitro evidence of their antimicrobial activity against coronaviruses (Chen et al., 2004). Other recurrent medicinal plants found in anti-coronavirus TCM remedies are *Saposhnikovia divaricata*, *Atractylodis macrocephalae*, *Lonicerae japonicae*, and *Forsythia Vahl* (Luo et al., 2020). As such, this could be a starting point for further research.

Overall, it is possible to identify two possible research streams to follow in the pursuit of finding useful phytotherapic compounds to fight infections caused by coronaviruses:

- Herbal remedies with a potentially preventive effect, mainly acting through a general boost of the immune system. Some examples can be *Astragalus membranaceus* or *Echinacea purpurea* (Block & Mead, 2003). Interestingly, astragalus was often added in TCM herbal formulas against SARS (Liu et al., 2012). *Uncaria tomentosa* and polysaccharides from medicinal mushrooms may be other options to study, due to their immunomodulatory properties. It might be also useful to test whether there are herbal compounds, which can be used as adjuvant in addition to a future vaccination.
- Herbal remedies with a potentially therapeutic effect, acting through different mechanisms on viral penetration and replication. Pharmacological derivatives of *Cinchona* bark, like chloroquine, have been already considered as possible drugs (Li & De Clercq, 2020). Reviews of clinical studies have suggested the efficacy of specific plant extracts from *Sambucus nigra*, *Pelargonium sidoides*, or *Cistus incanus* for the treatment of infectious respiratory ailments, regardless of their etiology (Agbabiaka, Guo, & Ernst, 2008; Hawkins, Baker, Cherry, & Dunne, 2019; Kalus et al., 2009). For polyphenols of sambucus and for pelargonium, an antiviral activity against human coronaviruses has been demonstrated in laboratory studies (Michaelis, Doerr, & Cinatl Jr., 2011; Weng et al., 2019), and researchers may consider them for further investigations in addition to the above mentioned liquorice and scutellaria. Recently, an array of 13 plant-derived substances has been identified as a set of compounds with in-vitro anti-SARS-Cov action, including cryptotanshinone, kaempferol, and quercetin (Zhang, Wu, Zhang, Deng, & Peng, 2020). Plant-derived substances appear to act at different stages of viral penetration and replication, for example binding the viral spike protein or inhibiting SARS-3CLpro activity (Yang et al., 2020). These findings can be used to expand the list of plant-based products to be considered eligible for future experiments. It might be also useful to test whether there are herbal compounds capable of reducing the period during which an infected subject remains contagious for limiting the disease spread. Additionally, phytotherapy can have an important role in the prevention and/or management of adverse effects of conventional drugs (Yang et al., 2020).

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In conclusion, phytotherapy research can help to explore potentially useful remedies against coronaviruses, and further investigations are recommended to identify and test all possible targets. Globally, herbs with some preliminary evidence of antiviral activity against coronaviruses, along with phytotherapic remedies with immune stimulant properties, appear as good candidates for additional studies on the topic.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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