# Green Solvents, Plant Metabolites, and COVID-19: Challenges and Perspectives

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Acquisition and isolation of value-added substances from natural sources using new types of green solvents are becoming a breakthrough area of 21st century research. In combination with various extraction techniques, there is expected to be a diversification of the use of these solvents for extraction, separation, and the formation of new drug carriers, allowing increased solubility of substances having potential pharmacological properties. Extraction, separation, or increase in the solubility of suitable drug candidates against COVID-19, or other viral diseases, opens new ways to effectively prevent and protect human health in this pandemic period.

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## Introduction

The deep roots of the use of medicinal plants and their extracts as natural medicines are based on the knowledge of individual cultures, spiritual traditions, and experience from therapeutic practice. During the development of civilization, the accumulated knowledge and application of medicinal plants were influenced mainly by Eastern cultures from China, India, Mesopotamia, and later by Greece, the Roman Empire and the Arab world. Especially in difficult historical periods, folk therapeutic methods and the use of medicinal plants were the only ways to maintain the health of the human population. Nowadays, it is becoming more and more frequent and clear that medicinal plants have a strong position also in modern medicine. It turns out that the human race is returning to the old experience and knowledge of the application of medicinal plants in conjunction with professional medicine. A large increase in the introduction of traditional plant resources, especially recently, is associated and supported by the development of new extraction methods and the use of new green extraction reagents, namely deep eutectic solvents (DESs) (Jablonský *et al.* 2018; Jablonský and Šima 2019).

Research and implementation of natural medicines are also motivated by the emergence of new diseases, such as viral COVID-19. The substances found in medicinal plants are natural and are therefore considered to be the most reasonable to use. Plants contain a wide range of viral protein inhibitors, which are usable in the treatment of viral-type diseases such as SARS. In general, plants can produce metabolites that exhibit inhibitory effects on enzymes, proteins, and virus propagation (Azim *et al.* 2020a,b; Banik *et al.* 2020; Bhuiyan *et al.* 2020). The herbal immune system is a complex system that can detect and inactivate invading pathogens with various tools. More than 450 plants and natural compounds have been shown to act as antivirals against SARS-CoV and similar viruses (Fuzimoto and Isidoro 2020). The various types of secondary metabolites are

bioactive species, and some of them have exhibited activity against coronavirus. These include 3-chymotrypsin-like protease, RNA-dependent RNA polymerase, papain-like protease, spike protein, angiotensin-converting enzyme II receptor or affect the life cycle of a coronavirus (Fuzimoto and Isidoro 2020; Banik *et al.* 2020).

The analysis of ADME (absorption, distribution, metabolism, and excretion) and obtaining pharmacokinetic/pharmacodynamics characteristics of isolated compounds from herbs/plants are key parameters for further progress and spreading of a breakthrough method for the acquisition of biologically and pharmacologically active compounds (Azim *et al.* 2020a,b; Jablonský *et al.* 2017; 2019).

Various extraction techniques can be used to isolate secondary plant metabolites. The selection and evolution of new extraction systems in conjunction with various extraction techniques leads to the acquisition of value-added substances of varying quality, purity and yield (Jablonský *et al.* 2018). Herbs, as a natural source of natural antiviral substances, can be important both in the prevention and protection of health against viral diseases (Jablonský *et al.* 2017; Azim *et al.* 2020a,b; Banik *et al.* 2020; Bhuiyan *et al.* 2020). In addition, isolated antiviral compounds can be used to modify various types of materials, thereby preventing the virus from spreading in the environment.

Green solvents with different substances have shown excellent pharmacological *in-vitro* properties (Rozema *et al.* 2015). They have different physical/chemical properties such as sustainability, acceptable toxicity, biodegradability, recyclability, relatively high ability to solubilize plant components, and extractability of these components. These properties may vary according to the composition of the solvents and the individual DES/NADES components' ratio (Jablonský *et al.* 2018; Jablonský and Šima 2019). In recent decades, there has been an increase in the usage of DES/NADES to extract drugs from plants and also to increase the solubility of individual drug candidates that exhibit anti-viral, anti-cancer, anti-allergic, anti-bacterial, anti-oxidant properties, or to form polymeric or self-assembled drug carriers (Emami and Shayanfar 2020).

Recent studies show that green solvent systems increase the solubility of natural products or drug candidates compared to conventional solvent systems (Morrison *et al.* 2009; Durand *et al.* 2017; Shamseddin *et al.* 2017; Jablonský *et al.* 2018; Jablonský and Šima 2019; Jeliński *et al.* 2019; Mokhtarpour *et al.* 2020).

## Challenges and Perspectives

Research should focus on selecting the most suitable plant-derived anti-viral/anti-coronavirus compounds, their extraction by environmentally friendly methods and extractants (DESs), and verifying extracts or extracted individual substances in terms of their effect against coronavirus COVID-19. Fortunately, the plants provide an ultimate, natural source of enzyme and viral propagation inhibitors to be implicated for treatment of disorders caused by SARS-CoV and SARS-CoV-2. The proposal of novel drugs and approaches for effective treatment of the novel coronavirus is essential after the rapid outbreak and spread of the disease. Studies of toxicity, side effects, and especially drug resistance are essential in order to use these systems in modern medicine (Cheuka *et al.* 2017). Important questions for further development are as follows:

- What is the interaction between solute natural products/drugs and DESs?
- What is the functionalization and storage tendency of natural drugs in green solvents?
- What is the knowledge of thermodynamic behavior and transport characteristics of green solvents, or their prediction?

- What data concerning the basic characteristics and their prediction for the creation of a macroscopic model must be entered (viscosity, density, solubility, reactivity, polarity)?
- How do the water content and changes in the macroscopic properties of the solvent influence the solubility of active substances and their properties?
- How will the stability of green solvent systems and dissolved drugs be ensured?

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