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The potential of South African medicinal plants for the treatment of COVID-19

Namrita Lall

Department of Plant and Soil Sciences, Faculty of Natural and Agricultural Sciences, University of Pretoria, Pretoria, South Africa
School of Natural Resources, University of Missouri, Columbia, MO, United States
College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India

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1. Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV-2), currently the cause of coronavirus disease of 2019 (COVID-19), has been declared a pandemic. Currently, not many antiviral treatments are available to effectively treat COVID-19 and therefore ongoing waves of increasing infection numbers and deaths have been reported globally. The current repurposing of drugs has been investigated as possible treatment by researchers and includes remdesivir and ivermectin. Many natural products have been selected and investigated for their potential inhibitory activity against SARS-CoV-2, especially those that have previously been identified to have inhibitory activity against SARS-CoV. There are several genetic similarities between SARS-CoV-2 and SARS-CoV, such as their similarities in the genome, the main protease crystal structure and the primary host receptor (Kaur *et al*., 2021).

2. Natural products as treatment options for SARS-CoV-2 (COVID-19)

Medicinal plants and their secondary metabolites from across the globe have been identified for their potential against human coronaviruses. These include *Artemisia annua* (Sweet wormwood), found natively in Asia and has shown inhibition against SARS-CoV-1 (IC_{50}: 34.5 ± 2.6 µg/ml, albeit through an unknown mechanism of action or associated with an unknown active constituent (Li *et al*., 2005). This has highlighted other species within the Artemisia genus to be investigated for their inhibitory potential against COVID-19. Another lead plant *Paulownia tomentosa* (Princess tree) is mainly found in Europe and was also found to have inhibitory activity against SARS-CoV-1 with activity ranging from 5-12.5 µM (Cho *et al*., 2013). Another Chinese plant of interest with good activity is *Lycoris radiata* also known as the red spider lily. This plant was also tested against SARS-CoV-1 and found to have an IC_{50} value of 15.7 ± 1.2 nM (Li *et al*., 2005). *Tylophora indica* (Indian Ipecac), has been tested for its inhibition potential through CoV-infected swine testicular cells. The inhibitory concentration (IC_{50}) was found to be 20 ± 1 nM. The activity has been linked to the active compound 7-methoxycryptopleurine and hypothesized to have a mechanism of action related to the inhibition of viral replication (Yang *et al*., 2010). No clinical trials investigating inhibition against SARS-CoV-2 have been planned as of yet, although crowdfunding has been initiated to investigate the potential of *Artemisia annua* as a possible treatment. Species from the *Helichrysum* genus have also been indicated for their inhibition potential against MERS-CoV 3C like protease (Jo *et al*., 2019).

3. Computational techniques to identify potential anti-COVID-19 metabolites from plants

The crystal structures of the main enzymes involved have been reported and most recently the crystal structure of the SARS-CoV-2 main protease (Mpro/3CLpro) (Zhang *et al*., 2020). The possible identification of compounds with inhibitory activity against SARS-CoV-related proteins is now possible as the crystal structures of key enzymes are reported. Computational studies are a high throughput system that can identify compounds with inhibitory activity against COVID-19 without any lab access required. In this manner, many possible similar structures and repurposed drugs can be identified. A molecular docking study was conducted for potential lead candidates that could inhibit Mpro. Several natural compounds such as kaempferol, quercetin, luteolin7-*o*-glucoside, naringenin, desmethoxycurcumin, curcumin, pigenin-7-*o*-glucoside, oleuropein, catechin and epicatechin-gallate showed inhibition potential against SARS-CoV-2 Mpro (Khaerunnisa *et al*., 2020). Computational studies done by Chen and Du (2020), also identified natural compounds with the potential to inhibit SARS-CoV-1 ACE2 receptors. These included baicalin, scutellarin, hesperetin, nicotianamine and glycyrrhizin (Chen and Du, 2020). Although, computational studies ensure rapid identification of target compounds, *in vitro* and *in vivo* experimental follow-up studies are required to confirm the data found during molecular docking studies.

4. The potential of South African natural products

Several plants from South Africa have recently been identified based on their previously identified antiviral activity and also those used traditionally for the treatment of symptoms associated with respiratory infections of a viral origin such as influenza. Several secondary metabolites with potential antiviral, anti-inflammatory and immunomodulatory activity have also been identified for their potential against SARS-CoV-2 infection.

Currently, 70% of the population are dependent on medicinal plants and the traditional use thereof for their primary healthcare needs (Scott *et al*., 2004). The country has huge potential for identifying novel compounds to treat many diseases. South African plants for

various purposes such as infectious diseases, cancer, skin hyperpigmentation problems, melasma, periodontal diseases, and acne have been scientifically investigated. Many South African plants have been identified for investigating their potential inhibition of SARS-CoV-2 infection. This in part due to their traditional usage for symptoms related to COVID-19 such as fever and coughing. A complete list of these plants has been identified by Verma *et al*. (2020). As mentioned, many of these plants have never before been tested for their inhibitory potential against SARS-CoV-2 or even SARS-CoV. A molecular docking analysis conducted by Dwarka *et al*. (2020), investigated compounds selected from a list of South African medicinal plants and their inhibitory potential against SARS-CoV-2 RdRp, 3CLpro and SAR-CoV-2 RBD. Arabic acid, an active compound found in *Acacia senegal*, was found to have the best docking score (–5.2 kcal/mol) against 3CLpro. Hypoxide, found in *Hypoxis hemerocallidea*, had a favourable docking score of –6.9 kcal/mol against SAR-CoV-2 RBD, whereas uzarin a main compound found in *Xysmalobium undulatum*, had the best docking score of –3.5 kcal/mol of all compounds tested against SARS-CoV-2 RdRp.

COVID-19, caused by SARS-CoV-2, has been identified as a global health concern, with research required on many different levels and areas to assist in alleviating the infection numbers and associated impacts suffered by billions of people worldwide. Incorporating molecular docking analysis and investigation into natural products may assist in additional treatment options available. Vast potential exists for new antiviral or adjuvant leads from South Africa, also known as a biodiversity hotspot for the variety of flora found. Journals such as **Annals of Phytomedicine: An International Journal** play a major role in the dissemination of important information such as the potential that botany plays in treating infectious diseases and viral pandemics such as COVID-19. Botany encompasses a wide variety of themes and areas. Through, journals such as 'Annals of Phytomedicine: An International Journal' all such important topics are covered in depth and in an accurate way.

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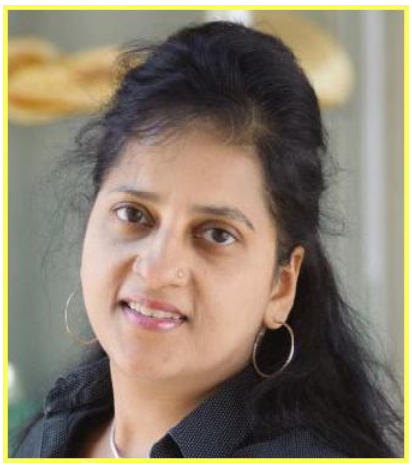

Professor Namrita Lall

NRF /DST Research Chair: Plant Health Products from IKS

Department of Plant and Soil Sciences, Faculty of Natural and Agricultural Sciences, University of Pretoria, Pretoria, South Africa

Biography

Professor Lall is a Research Chair at the University of Pretoria and has been placed in the Essential Science Indicators list of the top 1% of publication outputs (citations) in the discipline Pharmacology and Toxicology. She has been also appointed as an adjunct Professor at the School of Natural Resources University of Missouri, USA (Department is 1 of the top 15 in the world), at JSS AHER, India and as a Senior Research fellow at the Bio-Tech R&D Institute, Jamaica.

Six start-up companies named, "Bio Indigenous Solution" (a Mamelodi community-based company in Pretoria), "Blyde Botanics", "Anoiksen", "Scholareview", "Tone Tribe" and "Looksci" (formed by Young Postgraduates) resulted from Professor Lall's research programme.

She has international recognition for her research into the potential of medicinal plants for pharmaceutical and cosmeceutical purposes. One pharmaceutical product for skin-hyperpigmentation problem has been commercialized internationally and another twelve are close to commercialization.

She has published more than 165 research articles, 12 patents, 53 book chapters, H-index is 41 and RG score is over 40 (Top 5%). Three books on medicinal plants edited by Professor Lall, have been published by the publishers; 'Elsevier' and 'Taylor and Francis'.

Among several awards received in recognition for her work, a few are "**The Order of Mapungubwe",** South Africa's highest honour from the Honorable South African President Jacob Zuma (April 2014), and UNESCO-L'Oreal Award for Women in Science (one of the 10 selected candidates internationally, March 2002, in Paris).