

# Pre-print

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## MEDICINAL PLANTS IN RESPONSE TO COVID-19 IN MOZAMBIQUE: are they promising for a cure?

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**A ser publicado na:** Rev. cient. UEM: Sér. ciênc. bioméd. saúde pública - ISBN 2307-3896

**Data de submissão:** 27/07/2020

**Data de aceitação:** 25/08/2020

**Data de publicação:** xx/xx/xxxx

**Como citar este artigo:** HLASHWAYO, D. F., BARBOSA, F. M. A, MASSINGUE, A. Medicinal plants in response to COVID-19 in Mozambique: are they promising for a cure? **Rev. cient. UEM: Sér. ciênc. bioméd. saúde pública.** *Pre-print*, 2020.

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Artigo de revisão

## MEDICINAL PLANTS IN RESPONSE TO COVID-19 IN MOZAMBIQUE: are they promising for a cure?

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**ABSTRACT:** The COVID-19 pandemic caused by SARS-CoV-2 has been causing several deaths worldwide. So far, there is still no effective treatment for the disease. Under the monitoring of the World Health Organization, efforts are being made globally in order to develop vaccines and antiviral drugs that will provide effective prevention and treatment schemes. In Mozambique, a total of 3.395 cases and 20 deaths were reported until August 24, 2020. Bearing in mind that traditional medicine is still a predominant practice in the country, the role of medicinal plants in the prevention and/or treatment of COVID-19 should be carefully analyzed. In this article we reflect on the role of medicinal plants in response to COVID-19 in Mozambique.

**Keywords:** COVID-19, medicinal plants, Mozambique, SARS-CoV-2.

## PLANTAS MEDICINAIS COMO RESPOSTA AO COVID-19 EM MOÇAMBIQUE: serão promissoras para a cura?

**RESUMO:** A pandemia da COVID-19 causada pelo SARS-CoV-2 tem causado várias mortes em todo o mundo. Até o momento, ainda não existe um tratamento eficaz para a doença. Sob o monitoramento da Organização Mundial da Saúde, esforços estão sendo feitos globalmente com o fim de desenvolver vacinas e medicamentos antivirais que proporcionem meios de prevenção e tratamento eficazes. Em Moçambique, um total de 3.395 casos e 20 mortes foram relatados até o dia 24 de Agosto de 2020. Tendo em consideração que a medicina tradicional ainda é uma prática predominante no país, o papel das plantas medicinais na prevenção e/ou tratamento do COVID-19 deve ser cuidadosamente analisado. Neste artigo refletimos sobre o papel das plantas medicinais em resposta à COVID-19 em Moçambique.

**Palavras-chave:** COVID-19, plantas medicinais, Moçambique, SARS-CoV-2.

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## INTRODUCTION

The global pandemic of the novel coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has been the cause of a major concern worldwide, considering its rapid spread and the severity of the disease that can result in death. Globally, as of August 24, 2020, there have been 23.311.719 confirmed cases of COVID-19, including 806.410 deaths, reported to the World Health Organization (WHO) (<https://covid19.who.int/>).

SARS-CoV-2 infection, mainly transmitted through inhalation of infectious aerosols, can cause fatal disease or even asymptomatic carriage. In a recent exposure, the most common symptoms of COVID-19 are fever, sore throat, fatigue, cough or dyspnea. Elderly patients are often affected with pneumonia resulting from lower respiratory tract infection, and this may lead to death (CHAN *et al.*, 2020).

The currently used diagnostic tests for SARS-CoV-2 infection are reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP). The commonly analyzed samples are nasopharyngeal and oropharyngeal specimens (ZHAI *et al.*, 2020).

As a way to contain the spread of COVID-19, the President of the Republic of Mozambique has decreed a state of emergency that started on April 1, 2020 (MOÇAMBIQUE. DECRETO PRESIDENCIAL n.º 11/2020). This has included measures such as suspension of classes in all public and private schools from pre-school to university education; limiting the internal circulation of people; limiting the entry and exit of people from the national territory, among other measures. These measures allowed to delay the peak of the pandemic, keeping the pressure on health systems low, while waiting for effective treatments or vaccines. So far, the country has reported 3.395 confirmed cases and 20 deaths (<https://covid19.who.int/region/afro/country/mz>).

To date, there is no such specific drug or vaccine for the treatment and prevention of COVID-19. The treatment schemes include the use of known and commercially available drugs. Currently, for clinical management of mild COVID-19, WHO recommends a symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration. For severe COVID-19, WHO recommends administration of supplemental oxygen therapy to any patient with emergency signs, as well as to any patient without emergency signs and peripheral capillary oxygen saturation (SpO<sub>2</sub>) lower than 90%. There are also other treatment schemes dependent on the severity of the illness (WHO, 2020a).

Several research teams worldwide are conducting studies with the aim of developing effective drugs and vaccines against SARS-CoV-2. Thus, many clinical trials are ongoing. Until August 24, 2020, a total of 2.360 ongoing and completed studies on COVID-19 were listed on the WHO's International Clinical Trials Registry Platform (WHO ICTRP) ([https://clinicaltrials.gov/ct2/who\\_table](https://clinicaltrials.gov/ct2/who_table)). While these trials are ongoing, preventive measures are being implemented by the countries. Nevertheless, there is a rapid urgency for an effective prevention and treatment response to the SARS-CoV-2.

### **MEDICINAL PLANTS IN RESPONSE TO COVID-19: examples of other countries**

The WHO recognizes the role of traditional medicine in the treatment of diseases. To this end, one of the objectives of the WHO's traditional medicine strategy is to promote universal health coverage, integrating traditional and complementary services into health care service delivery and self-health (WHO, 2013). The WHO welcomes innovations including repurposing drugs, traditional medicines and developing new therapies aiming at the search for potential treatments for COVID-19. However, it is critical to establish their efficacy and safety through rigorous clinical trials (WHO, 2020b).

Worldwide, various plants and chemical compounds have been tested for activity against SARS-CoV-2 (AANOUS *et al.*, 2020; AHMAD *et al.*, 2020; AZIM *et al.*, 2020; BORKOTOKY and BANERJEE, 2020; CHIKHALE *et al.*, 2020; MIRZAIE *et al.*, 2020; MURUGAN, PANDIAN and JEYAKANTHAN, 2020; TRIPATHI *et al.*, 2020; UL QAMAR *et al.*, 2020). Furthermore, plants and their compounds are being used for the development of masks and other products with the aim of preventing infections (BALACHANDAR *et al.*, 2020).

Asian countries, such as China and India are very advanced in phytotherapy research, so much that they have natural products databases containing details about several phytochemicals, including their 2D and 3D structures. Some of these phytochemicals have antiviral properties. Studies using these databases are making computational predictions of the anti-SARS-CoV-2 effect of these phytochemicals. As a result of this, some of the main hits that may inhibit SARS-CoV-2 have already been reported (AHMAD *et al.*, 2020; AZIM *et al.*, 2020; BORKOTOKY and BANERJEE, 2020; CHIKHALE *et al.*, 2020; MURUGAN, PANDIAN and JEYAKANTHAN, 2020; TRIPATHI *et al.*, 2020; UL QAMAR *et al.*, 2020).

Plants such as *Nigella sativa* L. (AHMAD *et al.*, 2020) and *Azadirachta indica* A.Juss. (BORKOTOKY and BANERJEE, 2020) have already been proven to have phytochemical potential in combating

SARS-CoV-2. Some phytochemicals that are promising anti-SARS-CoV-2 agents are present in many plants, such as: *Amaranthus tricolor* L., *Camellia sinensis* (L.) Kuntze, *Fraxinus sieboldiana* Blume, *Glycyrrhiza uralensis* Fisch., *Hyptis atrorubens* Poit., *Myrica cerifera* L., *Phaseolus vulgaris* L., *Phyllanthus emblica* L. and *Psoralea argyrea* (A.Gray) Barneby (UL QAMAR *et al.*, 2020).

In India, after the Central Council for Research in Homoeopathy discussed the ways and means of prevention of SARS-CoV-2 infection through homoeopathy, the Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), has published a list of preventive and prophylactic medicinal plants for COVID-19 that shall be used in consultation with registered Ayurveda practitioners (INDIA. MINISTRY OF AYUSH, 2020). With this, the efforts that governments and research teams are making to integrate herbal medicine in the health care of COVID-19 are noteworthy. However, as recommended by the WHO, care should be taken with the use of herbal medicines, as these must be validated for the intended use.

### MOZAMBIQUE CONTEXT ON MEDICINAL PLANTS IN RESPONSE TO COVID-19

In Mozambique, the practice of traditional medicine is common due to several factors, including the insufficient coverage of the national health services. It is estimated that 60% of the population in the country uses traditional medicine services for primary health care (RESOLUÇÃO Nº 11/2004). In the national context, traditional medicine is mainly characterized by the use of medicinal plants (WHO, 2019).

The Mozambican flora has about 5.500 plants. Of these, 10% to 15% are used in traditional medicine (BANDEIRA, GASPAS and PAGULA, 2001; KROG, FALCÃO and OLSEN, 2006). It is likely that in this flora there are plants with activity against SARS-CoV-2, given the fact that phytochemicals are a major source of bioactive compounds with antiviral and other pharmacological properties (BEN-SHABAT *et al.*, 2020). So far, to our best knowledge, there is no study published in Mozambique on the antiviral activity of native plants on SARS-CoV-2, or even any other pharmacological study on native medicinal plants in the treatment of COVID-19. Thus, there is still a lot to explore in the country.

Following a conventional ethnopharmacological approach, for screening of plants for the prevention and/or treatment of COVID-19, the first step would be to identify the medicinal plants used to treat respiratory diseases, due to the fact that SARS-CoV-2 affects the respiratory system. To date, there is still no compilation of these plants, but some studies report plants used for this purpose (JANSEN and MENDES, 1983, 1984, 1990, 1991; VERZÁR and PETRI, 1987; BANDEIRA, GASPAS and PAGULA, 2001; JANSEN, DA SILVA and MENDES, 2001; RIBEIRO *et al.*, 2010; BARBOSA *et al.*, 2020) and there are probably other reports that have not been published in indexed articles.

Some examples of plants used for treatment of respiratory diseases in Mozambique are the following: *Acacia nilotica* (L.) Delile, *Adenia gummifera* (Harv.) Harms, *Aloe marlothii* A.Berger, *Annona senegalensis* Pers., *Ansellia africana* Lindl, *Blepharis diversispina* (Nees) C.B.Clarke, *Capparis tomentosa* Lam., *Cissus quadrangularis* L., *Cleistochlamys kirkii* (Benth.) Oliv., *Elephantorrhiza elephantina* (Burch.) Skeels, *Euclea natalensis* A.DC., *Garcinia livingstonei* T.Anderson, *Grewia sulcata* Mast., *Guibourtia conjugata* (Bolle) J.Leonard, *Gymnanthemum coloratum* (Willd.) H.Rob. & B.Kahn, *Lannea schweinfurthii* var. *stuhlmannii* (Engl.) Kokwaro, *Lippia javanica* (Burm.f.) Spreng., *Margaritaria discoidea* (Baill.) G.L.Webster, *Myrothamnus flabellifolia* Welw., *Ochna natalitia* (Meisn.) Walp., *Opuntia ficus-indica* (L.) Mill., *Opuntia* sp, *Ozoroa insignis* subsp. *reticulata* (Baker f.) J.B.Gillett, *Rauwolfia caffra* Sond., *Securidaca longipedunculata* Fresen., *Tabernaemontana elegans* Stapf and *Warburgia salutaris* (G.Bertol.) Chiov. (VERZÁR and PETRI, 1987; BANDEIRA, GASPAS and PAGULA, 2001; RIBEIRO *et al.*, 2010; BARBOSA *et al.*, 2020).

Within the wide range of medicinal plants used to treat respiratory diseases in Mozambique, the next step would be to analyze *in vitro* the activity of plant extracts on SARS-CoV-2, and to identify the phytochemicals present in the effective plants. The identification of the active compounds, their isolation *in vitro* and testing for antiviral activity would be crucial steps to be taken, in order to identify the chemical compounds responsible for such activity. Subsequent studies at *in vivo* models could be carried out afterwards in order to elucidate the biological mechanisms and pharmacological properties of the isolated compounds. This would contribute to the validation of the use of the identified plants in the alternative treatment of COVID-19.

Poor research in phytotherapy is a major contributor to the lack of scientific evidence to recommend the use of plants for the treatment of COVID-19 in Mozambique, as we lack pharmacopoeias, monographs and laboratory studies that prove the antiviral effect of native plants extracts. However, this can be an opportunity for institutions working with herbal medicine research in Mozambique to join forces to start developing pharmacopoeias and apply research jointly to solve public health issues in Mozambique.

In addition, it is necessary to reflect on the local capacity for quality and efficacy certification of the herbal medicines, which requires human and financial resources and complex procedures (PARVEEN *et al.*, 2015). The quality and efficacy certification implies analysis of raw materials and excipients, toxicity, therapeutic action and pharmacokinetics of the product, involving non-clinical and clinical trials. Clinical trials are the most expensive and complex phase in this process. However, it is possible to carry out those studies in Mozambique, once a funding is obtained. It is known that the country has already carried out several clinical trials, although not in the field of phytotherapy (JULIEN *et al.*, 1999; ALONSO *et al.*, 2005; NHAMA *et al.*, 2014; HEMMINKI *et al.*, 2016; SANCHEZ *et al.*, 2020).

After proving the efficacy of a medicinal plant in the treatment of COVID-19, special attention should be given to avoid over-exploitation in the natural habitat. Therefore, agronomic studies are needed to obtain information about the cultivation of these plants and to be able to propagate in environments other than their natural habitat.

With the beginning of the report of the first cases of COVID-19 in Mozambique, the trade of eucalyptus leaves was installed across the country, considering them preventive. Eucalyptus is known to be used to clear the nasal passages through "*bafo*", or inhalation of the vapor of boiled leaves<sup>1</sup>. However, the lack of scientific validation puts at risk the use of this therapeutic approach (YANG, 2020), since plants can have toxic compounds, and depending on the dosage, cause serious damage to health (GUPTA and RAINA, 1998) or may even have no effect on the virus or symptoms.

Another point of view in which plants can be analyzed as a potential to contribute to the prevention and/or treatment of COVID-19 consists of nutraceuticals. Although there is still no internationally recognized definition of a nutraceutical, it can be defined as 'a dietary supplement, food or medical food that has a benefit which prevents or reduces the risk of a disease or health condition, including the management of a disease or health condition or the improvement of health; and is safe for human consumption in the quantity, and with the frequency required to realize such properties' (ARONSON, 2017).

Studies already point to the benefit of nutraceuticals in prevention and management of COVID-19 (JAYAWARDENA *et al.*, 2020; KUMAR and JENA, 2020), such as folic acid alone or with combination with its derivatives tetrahydrofolic acid and 5-methyl-tetrahydrofolic acid, which were tested in a virtual screening and revealed as potential molecules against SARS-CoV-2 (KUMAR and JENA, 2020).

The role of functional foods rich in nutraceuticals on COVID-19 was analyzed as well. For example, garlic (*Allium sativum*) revealed to play an important role in increasing immune system

cells and repressing the production and secretion of proinflammatory cytokines and the leptin hormone. Thus, this plant was considered an acceptable preventive measure against COVID-19 and it relieves some symptoms detected in the disease (DONMA and DONMA, 2020).

Analyzing the Mozambican context, where malnutrition predominates in 27.9% of the population and food insecurity in 42.5% (FAOSTAT, 2020), the consumption of nutraceuticals can contribute to the strengthening of the immune system, improving the body's ability to respond to a possible infection by SARS-CoV-2.

Some medicinal plants of Mozambique are also used as food, mainly in rural areas. The research and dissemination of the benefits of eating these plants may constitute a resource for the use of the local flora to strengthen the immune system in order to aid the prevention and/or treatment of COVID-19. Some studies have identified such native plants rich in nutraceuticals as: *Adansonia digitata* L., *Amaranthus spinosus* L., *Landolphia kirkii* Dyer, *Momordica balsamina* L., *Salacia kraussii* (A.Rich.) Hochst., *Sclerocarya birrea* (A.Rich.) Hochst. and *Vangueria infausta* Burch. (OLIVEIRA and DE CARVALHO, 1975; MAGAIA *et al.*, 2013). Many other native plants are rich in nutraceutical compounds and their consumption should be considered by the population in order to strengthen the immune system.

Finally, while efforts are being made to find an effective treatment for COVID-19, in Mozambique, care should be taken regarding false information about plants and/or mixtures supposedly "miraculous" for treatment of the disease. The plants must have proof of quality, safety and efficacy. If there is no such proof, the health of consumers may be in danger, since plants may have a certain toxicity. In addition, this consumption of plants without proof of effectiveness, can confer a false sense of security, leading people to neglect other preventive measures such as constant hygiene and physical distance, which are crucial at this moment when waiting for an effective treatment.

## CONCLUSIONS

Mozambique has a wide flora of medicinal plants rich in phytochemical compounds. These compounds might have antiviral activity against SARS-CoV-2 that must be validated through *in vitro* and *in vivo* studies. In other countries of the world, studies have been carried out in order to validate the use of medicinal plants for prevention and/or treatment of COVID-19. However, this type of research is still lacking in this country.

Taking into account the great contribution of traditional medicine to basic health care in Mozambique, medicinal plants should be explored for their potential in the prevention and/or treatment of COVID-19, through adequate pharmacological studies. A quick way to identify plants for screening for their anti-SARS-CoV-2 action would be through plants that have been described as used to treat respiratory diseases through a literature review. Some of these plants were identified in this article.

On the other hand, the role of nutraceuticals in improving immunity was emphasized in this article. The consumption of foods rich in nutraceuticals will allow the organism to be able to defend itself against a probable infection. Mozambican flora has plants rich in nutraceuticals, some of which are medicinal and others are used as food. The COVID-19 pandemic also raises the need to conduct ethnobotanical studies in order to record knowledge about the use of plants, with a view of using this knowledge in the future to conduct laboratory studies for the discovery of new and effective drugs.

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## NOTES

<sup>1</sup> <https://clubofmozambique.com/news/covid-19-race-to-eucalyptus-in-maputo-watch-157544/>