

Phytomedicines and nutraceuticals in the clinical management of COVID-19: Potentials and pitfalls

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ABSTRACT

COVID-19 has exposed what we have long-feared: Many countries in Africa have very fragile public healthcare delivery systems, out-dated clinical laboratory infrastructure, and inadequate home-grown biomedical research preparedness. These challenges that are an asterisk in the prevention and treatment of COVID-19 in Africa should become the new window of opportunity for novel drugs from indigenous African medicinal plants. Africa needs a drug discovery renaissance inspired by the potentials of the continent's huge endowment of medicinal plants. As a continent, Africa needs to invest in indigenous natural agents that inhibit entry of human coronavirus into cells. Africa should also develop natural products that block general replication and specific chymotrypsin-like protease-mediated replication of SARS-CoV-2. Turmeric, *Eucalyptus* essential oil, garlic, cinnamon plant, and *Ganoderma* mushroom are being used to offset the effects of COVID-19 in many parts of the world. Plant active compounds such as glycyrrhizin, iguesterin, resveratrol, homoharringtonine, tomentins A-E, sinigrin, silvestrol, and cinnamaldehyde have anti-COVID-19 actions. Due to current obstacles in the clinical management of COVID-19 in Africa, this paper advocates for the use of indigenous natural medicines to roll-back the pandemic.

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1 Introduction

Since the COVID-19 pandemic is exacerbating an already dire public health situation, Africa should place special emphasis on public health reforms that embrace Afrocentric drug discovery and development. Given the inadequate supplies of vaccines and drugs for COVID-19, indigenous natural products are low hanging fruits that should be harnessed as the new frontier against SARS-CoV-2 in Africa. Elsewhere, the use of phytonutrients and nutraceuticals has tremendously increased during the current COVID-19 pandemic.

In the absence of conventional therapies, more than 85% of COVID-19 patients in China were treated with Traditional Chinese Medicine (Chinsembu, 2020a). Jinchai, a capsule of Traditional Chinese Medicine, inhibits SARS-CoV-2. Jinchai deters the transcription and replication of SARS-CoV-2, relieves lung inflammation induced by SARS-CoV-2 infection, improves membrane lipid fluidity of SARS-CoV-2-infected cells, and impedes the release of the inflammatory factor nitric oxide, thereby reducing the degree of lung injury. In a rapid review of 28 Chinese guidelines, about 23% of plant medicines were used in the treatment of COVID-19 patients (Chinsembu, 2020a).

As COVID-19 reformats the classical norms of pharmaceutical and clinical interventions, the pandemic should serve as a poignant reminder that repurposing of indigenous African medicinal plants to treat COVID-19 should become part of the new African health vernacular. Comparative genomics lends credence to the repurposing of

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current anti-SARS natural products for the treatment of COVID-19 (Chinsembu, 2020a). This is because the genome sequence of SARS-CoV is very similar to that of SARS-CoV-2. In this new normal, locally-researched indigenous African natural products should become part of the COVID-19 survival kit. This is because nearly 75% of all the approved anti-infective drugs are derived from medicinal plants. Data on anti-human coronavirus inhibitors from medicinal plants are no longer anecdotal.

Of course, medicinal plant products are not a silver-bullet solution to the current global COVID-19 pandemic. Medicinal plants are not a substitute for the global push to develop pharmaceutical drugs and vaccines for COVID-19. However, natural products are complementary and alternative medicines that increase the options available to COVID-19 patients especially those in low-income settings in Africa. The scarcity of vaccines and pharmaceutical drugs means that the path out of this COVID-19 pandemic is still narrow for many African countries.

Africa should use this COVID-19 pandemic to view research through a new prism of economic botany that leverages the continent to dominate the global system of innovation for the discovery and development of novel COVID-19 drugs from indigenous medicinal plants. The search for novel drug molecules from natural products tallies into the new economic paradigm as global trade in herbal medicines is now estimated at more than US\$ 83 billion annually. A few years ago, the herbal medicines market in Europe was about US\$ 10 billion, US\$ 1.0 billion in India, and US\$ 4 million in the USA. Trade in herbal medicines in Germany alone accounts for over US\$ 3.5 billion; France, US\$ 1.6 billion; and Italy, US\$ 0.6 billion. China earns more than US\$ 14 billion per year in medicinal botanicals and drugs based on plant ingredients. The business of natural medicines is a going concern all over the world; it is a multi-billion dollar enterprise (Chinsembu, 2018).

African countries should seize this momentum in the global trade of herbal medicines to develop new COVID-19 drugs from the continent's indigenous plants. Even as many economies falter during the current pandemic, export trade in medicinal plants for COVID-19 can earn African countries billions of dollars to unlock and stimulate the continent's economies. Research institutions, academia, governments and the private sector in Africa, where 22% of the landmass is covered by forests, should reset their priorities, change direction and forge a new path of Afrocentric drug discovery so that Africa may become a global pioneer in the innovation of COVID-19 drugs from indigenous medicinal plants. Sadly, many African governments have paid lip-service to the discovery of novel drugs from indigenous African medicinal plants.

Africa needs a new generation of bio-entrepreneurs that can harness the continent's wealth of indigenous plant resources. To win the war against COVID-19, Africans need to go back to the fundamentals, to their indigenous knowledge of medicinal plants and functional foods (remember: food is the best medicine). It is in unsung indigenous foods as in natural products that Mother Nature has bequeathed the secret pharmacy of natural remedies against COVID-19. Without investing in drug development from African indigenous medicinal plants, Africa's COVID-19 prevention and treatment response programmes will continue to be built on a foundation of quicksand; the harder the continent tries to climb out of the pandemic, the deeper she sinks into the COVID-19 abyss. Unless Africa looks deeper into the past, the continent cannot go further into the future.

Is there experimental evidence that natural products work against COVID-19? Here is what we know about a few examples such as turmeric, *Eucalyptus* essential oil, garlic, cinnamon, and *Ganoderma* mushroom. These examples highlight the potentials and pitfalls of phytochemicals and nutraceuticals in the clinical management of COVID-19.

2 Turmeric

The dried rhizome of *Curcuma longa* is the source of turmeric, the widely used spice in foods. The turmeric-derived polyphenol curcumin was tested for therapeutic potential against SARS-CoV-2. *In vitro*, there was a higher binding affinity of curcumin versus nelfinavir to Mpro of SARS-CoV-2. Curcumin isolated from turmeric

irreversibly inhibited aminopeptidase N/CD13, demonstrating that curcumin could play a role in preventing and decreasing SARS-CoV-2 infection by inhibiting its cellular binding via CD13 (Pastor *et al.*, 2021). Curcumin inhibits SARS-CoV 3CL^{pro}, IC₅₀ value of 23.5 μM (Ryu *et al.*, 2010). Curcumin also acts by inducing the cell death of macrophages.

Earlier, Chinsembu (2016) stated that curcumin [1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione] is a phenolic compound that exhibits antimycobacterial activity. Curcumin also has antioxidant, anti-cancer and anti-inflammatory properties but is non-cytotoxic to normal human cells. These properties make curcumin a very attractive chemical ingredient to alleviate lung infections including tuberculosis and pneumonia, though it is relatively unstable and beset by poor bioavailability. The relatively low availability and rapid metabolism of curcumin may limit its clinical impact. Since curcumin is insoluble in water at pH 7 and not stable in acid or alkaline solutions, the bloodstream's net absorption is low, thus limiting systemic bioavailability and clinical efficacy (Pastor *et al.*, 2021).

The potential of curcumin to alleviate COVID-19 is reinforced by the fact that curcumin, like chloroquine, has moderate antimalarial activity, IC₅₀ of 5 – 18 μM (Chinsembu, 2015). Curcumin had potent activity against *Plasmodium berghei* and it was able to prevent cerebral malaria and delay death of animals by about 10 days. Notwithstanding, Chinsembu (2015) stated that the *in vivo* antimalarial efficacy of curcumin was reduced because 90% of curcumin was metabolized within 30 min, and due to its poor absorption, rapid metabolism and excretion, it was unlikely that substantial concentrations of curcumin were pharmacologically active in the body after ingestion.

3 *Eucalyptus* essential oil

Chaachouay *et al.* (2021) reported that eucalyptol, an essential oil from *Eucalyptus globulus* Labill., was an effective antiviral compound against COVID-19 because this major component of eucalyptus oil consists of ether (–O), ketone (=O), and hydroxyl (–OH) groups which exert the main inhibitory function against SARS-CoV-2. Note that essential oils insert non-specifically into the lipid bilayer, thus changing the conformation and fluidity of the viral cell membrane. *Eucalyptus* oil is used during steaming, a common anti-COVID-19 practice among Zambians. High temperature can cause irreversible denaturation of proteins and loss of SARS-CoV-2 infectivity; this is obtained after heating at 56 °C for 30 min in liquid environments (la Marca *et al.*, 2021). Repeated steam inhalation cycles can reduce the risk of progression to full blown infection if performed soon after contagion (la Marca *et al.*, 2021). Thus use of *Eucalyptus* leaves or essential oil is common during steaming for the prevention or treatment of COVID-19. In the North-Western Province of Zambia, the Lunda people in districts such as Zambezi and Mwinilung'a use a pleasantly scented herb commonly known as Lweng'i during steaming (Chinsembu, 2020b).

4 Garlic

The intake of garlic is being touted as a possible public health strategy to reduce COVID-19, and the mechanism of action for garlic has been postulated. Also called main protease (M^{pro}), the chymotrypsin-like protease (3CL^{pro}) of SARS-CoV mediates the proteolytic processing of replicase polypeptides 1a and 1ab into functional proteins (with amino acids such as Thr24, Thr26, and Asn119 present in the active site regions); hence it is an important target for drug development (Khubber *et al.*, 2020). Since M^{pro} is responsible for viral replication and the production of functional replicase during SARS-CoV-2 maturation, the infection rate may be substantially reduced by hindering the proteolytic processing of the viral replicase polyprotein.

Molecular docking studies demonstrated that alliin, an organosulfur compound, had higher antiviral potential to prevent COVID-19. A concentration of 0.1 mL of garlic clove extract blocked SARS-CoV-1 replication. The presence of organosulfur (e.g., allicin) and flavonoid (e.g., quercetin) compounds in aqueous extracts and essential

oils of garlic and their interaction with the M^{pro} protease causes a reduction in the rate of viral infection caused by SARS-CoV-2 (Khubber *et al.*, 2020). Quercetin blocks the M^{pro} present in SARS-CoV-1 during the replication in host cells by impeding viral attachment. As an anti-diabetic agent, garlic could also be very helpful in COVID-19 patients at higher risk due to diabetes (Chinsembu, 2019a).

5 Cinnamon plant

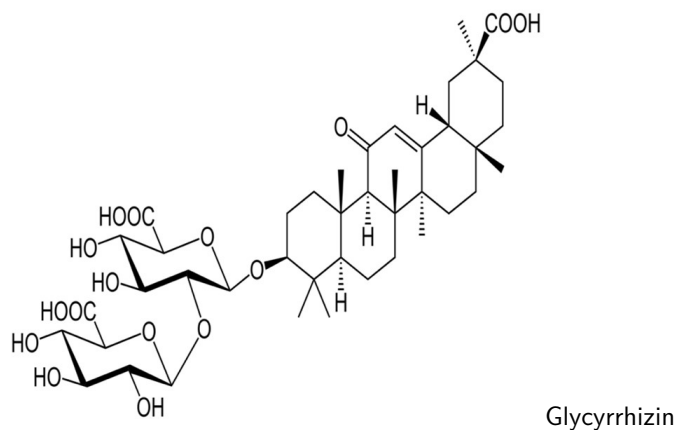
Chinsembu (2020a) reported that in oriental herbal medicine, the bark of the cinnamon plant *Cinnamomum cassia* (L.) J. Presl has been used as a spice, infusion and prime component of herbal remedies for common cold, gastrointestinal infections, cancer, chronic cardiovascular disease and gynecological disorders. Cinnamon bark extract is known to have anti-RNA viral effects. The cinnamon extract inhibits wild type SARS-CoV infection *in vitro* with an IC₅₀ of 43 μ M; and the proposed mechanism of action for cinnamon bark extract is blocking cell entry via endocytosis. Whereas antiviral, anti-bacterial and anti-cancer effects were attributable to essential oils such as cinnamaldehyde, the anti-inflammatory actions of cinnamon water extract are due to the presence of polyphenols such as flavonoids and tannins. Molecular docking studies show that cinnamaldehyde may block the attachment of SARS-CoV-2, though detailed *in vitro* and *in vivo* studies are required to confirm its efficacy.

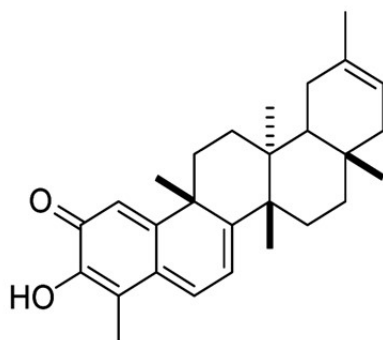
6 Ganoderma mushroom

The medicinal basidiomycete *Ganoderma lucidum* (Curtis) Karst. inhibited SARS-CoV RNA dependent RNA polymerase (RdRp) in a dose-dependent manner, IC₅₀ = 41.9 μ g/mL. An extract of *G. lucidum* was effective against SARS-CoV in a randomized, double-blind, placebo-controlled study.

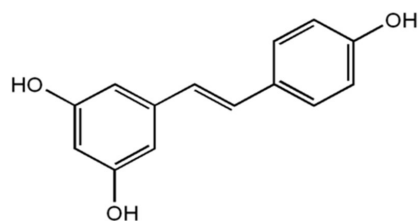
7 Plant active compounds possess anti-SARS-CoV-2 actions

Plant active ingredients such as glycyrrhizin, iguesterin, resveratrol, homoharringtonine, immunomodulatory compounds tomentins A-E, sinigrin, silvestrol, and cinnamaldehyde are very useful in ameliorating COVID-19 symptoms (Chinsembu, 2020a). The structures of these plant chemical compounds show that many of these compounds inhibit SARS-CoV-2 replication because their chemical structures mimic nucleoside analogues. While many of the natural products possess anti-SARS-CoV properties, their extracts and active compounds should be evaluated for human cytotoxicity and dosage (Chinsembu, 2020a). Putative anti-SARS-CoV-2 extracts and active compounds should be rigorously tested in animal and randomized placebo clinical trials (Chinsembu, 2020a).

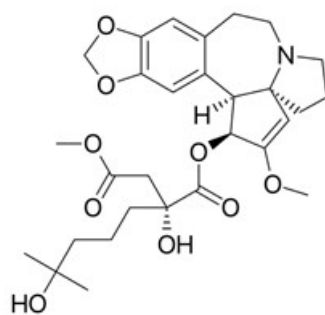




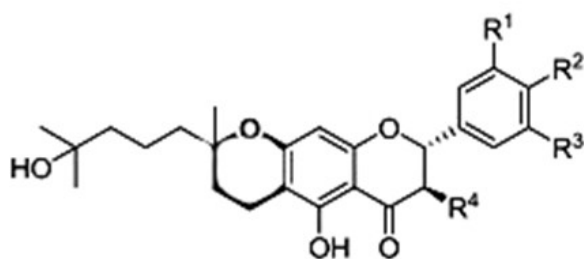
Iguesterin



Resveratrol

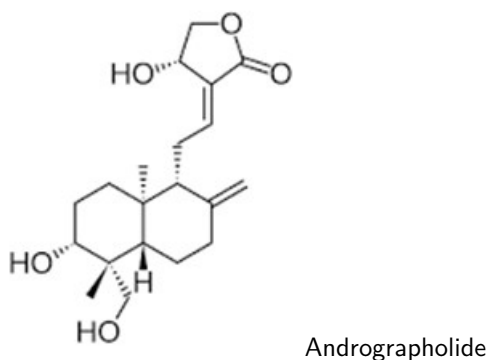
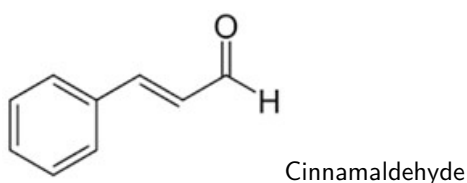
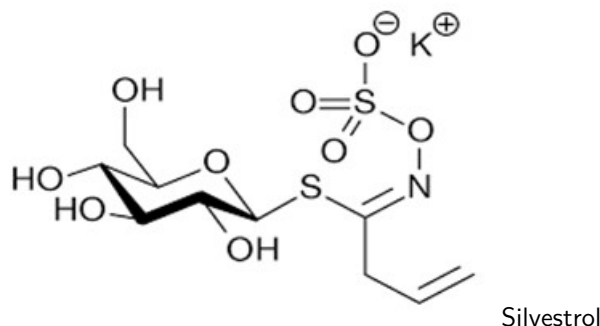


Homoharringtonine



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Tomentins A-E



8 Filter out pan-assay interference compounds (PAINS)

There is also need to filter out pan-assay interference compounds (PAINS). Indeed, the anti-SARS-CoV-2 therapeutic application of andrographolide is limited because this bioactive bicyclic diterpenoid is a highly promiscuous compound that interacts with numerous and unknown cellular targets; hence it is not seriously considered as a potential drug candidate (Chinsembu, 2019b). Thus, although high-throughput screening (HTS) is one of the most powerful approaches available for identifying new plant lead compounds (just as virtual and experimental HTS have accelerated lead identification and changed drug discovery), it has also introduced a large number of PAINS which turn out to be dead-ends after a great deal of time and resources have been spent. PAINS are frequent hitters (promiscuous compounds) that may render efforts to develop novel SARS-CoV-2 drugs from plant-derived compounds fruitless.

9 Conclusions and recommendations

Although turmeric, *Eucalyptus* essential oil and garlic may be useful in the clinical management of COVID-19, more research needs to be conducted on these three and other natural products. Like China, Africa should choose her own trajectory of self-reliant healthcare provision premised on the practice of indigenous citizen doctors and their medicinal plants. COVID-19 has shown that health systems in Africa are at the cusp of a new era. Recall

that the European Union is funding the *PharmaSea* Project, to comb the oceans and seas for novel natural products that can be converted into new pharmaceutical drugs to fight antibiotic resistant microbes, diabetes, cholesterol, hypertension and epilepsy.

Africa should also turn to its forests for novel molecules that can be converted into wonder drugs to treat COVID-19. Countries with access to the sea, for example Namibia, could also discover anti-COVID-19 drugs from their vast resources of marine algae and sponges. For example, *Spirulina platensis* (Gomont) Geitler is a microscopic filamentous alga rich in proteins, vitamins, essential amino acids, minerals and essential fatty acids like γ -linolenic acid. It is produced commercially and sold as a food supplement in health food stores around the world. *Spirulina platensis* (15 grams) enhances the immune status, inflammatory and oxidative markers of COVID-19 patients (Chinsembu, 2020a).

The benefits that accrue from the use of indigenous African medicinal plants will form the practical basis for transacting indigenous knowledge with the younger African generations that are so much immersed in Western lifestyles and culture. Within this microcosm, Africa ought to be hopeful that the future may be a continuation of the past, that the baton of indigenous knowledge of medicinal plants shall be passed on to the younger generations. This should provide a glimmer of hope that indigenous knowledge of botanical medicines and functional foods shall neither be a lost African civilization nor part of this man-made sixth extinction.

The health of Africans cannot be guaranteed if all COVID-19 drugs and vaccines in Africa are produced in Europe, America, China and India. The health of Africans should not be left to the whims of philanthropists and multinational companies in the big business of drugs and vaccines for COVID-19. While medicinal properties of natural products are profoundly and potently self-evident, the acceptance of natural remedies has never been self-imposing. To guarantee their basic healthcare needs, Africans must forge a new socio-cultural compact with indigenous natural products, the low-cost self-insurance scheme for the treatment of COVID-19.

The most notable research limitation is that many countries in Africa, Antarctica, Asia (except China), Australia/Oceania, Europe, North America, and South America lag behind in terms of research efforts on anti-coronavirus remedies from medicinal plants. In many countries all over the world, there is need to conduct detailed ethnobotanical studies to establish putative anti-SARS-CoV-2 medicinal plants and their active compounds. The search for new anti-SARS-CoV-2 agents should also be extended to marine organisms.

Finally, big multinational pharmaceutical companies (big pharma) should concede the point that proponents of indigenous natural medicines have more convincing and far-reaching clinical evidence and life experiences about the efficacy and safety of natural products. Stakeholders including indigenous knowledge holders, community of practitioners, researchers and patients alike must be clear-eyed on the curative prospects and constraints of natural products for COVID-19. Within African healthcare policies and programming, indigenous medicinal plants cannot be half in and half out. If there is a long-term remedy for COVID-19 in Africa, it must lie in Mother Nature's pharmacy of green medicines. Use of phytomedicines and nutraceuticals in the clinical management of COVID-19 is a daunting reality as much as it is a beautiful prospect.

References

- Chaachouay, N., Douira, A., Zidane, L., 2021. COVID-19, prevention and treatment with herbal medicine in the herbal markets of Salé Prefecture, North-Western Morocco. *European Journal of Integrative Medicine*, 101285.
- Chinsembu, K.C., 2015. Plants as antimalarial agents in Sub-Saharan Africa. *Acta Tropica* 152, 32–48.
- Chinsembu, K.C., 2016. Tuberculosis and nature's pharmacy of putative anti-tuberculosis agents. *Acta Tropica* 153, 46–56.
- Chinsembu, K.C., 2018. *Indigenous natural medicines for diabetes, obesity, and high cholesterol*. ISBN: 978-99945-60-92-9. Cesiks: Windhoek, Namibia, 250 pages.

- Chinsembu, K.C., 2019a. Diabetes mellitus and nature's pharmacy of putative antidiabetic plants. *Journal of Herbal Medicine* 15, 100230.
- Chinsembu, K.C., 2019b. Chemical diversity and activity profiles of HIV-1 reverse transcriptase inhibitors from plants. *Revista Brasileira de Farmacognosia (Brazilian Journal of Pharmacognosy)* 29, 504–528.
- Chinsembu, K.C., 2020a. Coronaviruses and nature's pharmacy for the relief of coronavirus disease 2019. *Revista Brasileira de Farmacognosia (Brazilian Journal of Pharmacognosy)* 30, 603–621.
- Chinsembu, K.C., 2020b. Chinsembu urges search for COVID-19 drugs from indigenous medicinal plants. *The Mast Newspaper*, 27 July 2020. <https://www.themastonline.com/2020/07/27/chinsembu-urges-search-for-covid-19-drugs-from-indigenous-medicinal-plants/>.
- Khubber, S., Hashemifesharaki, R., Mohammadi, M., Gharibzahedi, S.M.T., 2020. Garlic (*Allium sativum* L.): a potential unique therapeutic food rich in organosulfur and flavonoid compounds to fight with COVID-19. *Nutrition Journal* 19, 1-3.
- la Marca, G., Barp, J., Frenos, S., Mugelli, A., Galli, L., Calistri, E., ... Guerrini, R., 2021. Thermal inactivation of SARS COVID-2 virus: are steam inhalations a potential treatment?. *Life Sciences* 265, 118801.
- Pastor, N., Collado, M.C., Manzoni, P., 2021. Phytonutrient and nutraceutical action against COVID-19: current review of characteristics and benefits. *Nutrients* 13, 464.
- Ryu, Y.B., Park, S.J., Kim, Y.M., Lee, J.Y., Seo, W.D., Chang, J. S., ... Lee, W.S., 2010. SARS-CoV β CL^{pro} inhibitory effects of quinone-methide triterpenes from *Tripterygium regelii*. *Bioorganic & Medicinal Chemistry Letters* 20, 1873–1876.