Review Article

Fostering home-grown response to Covid-19: development of Improved Traditional Herbal Medicines to WHO Standards

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Abstract

Facing the unprecedented burden and rapid spread of the Covid-19 pandemic across the globe, responses from various regions have been exceptionally quick. Drug discovery has been essentially based on repurposing, particularly at the onset of the scourge. Several experimental models have been designed ranging from in vitro cell culture systems to nonhuman primates; however, each with advantages and limitations. It was revealed beside its detrimental consequences on health, economy and the society, Covid-19 has also provided opportunity to highlight the immense potential of traditional medicine as a valid alternative for addressing major health threat. The African traditional medicine has been instrumental for the control of the COVID-19 pandemic in the continent, in situation of extremely low vaccination coverage. For optimal and sustainable use of traditional medicine, we strongly recommend products be developed following the WHO standards, while taking into consideration sustainability, environmental protection and copyright issues surrounding the natural product-based drug research and development.

Keywords: Covid-19, Improved Traditional Herbal Medicine, WHO Standard, Cameroon

Résumé

Face au fardeau sans précédent et à la propagation fulgurante de la pandémie de Covid-19 à travers le monde, les réponses de diverses régions ont été exceptionnellement rapides. La recherche de solutions thérapeutiques a été essentiellement basée sur la « repurposing », en particulier au début du fléau. Plusieurs modèles expérimentaux ont été conçus allant des systèmes de culture cellulaire *in vitro* aux primates non humains ; cependant chacune avec ses avantages et ses limites. A côté de ses conséquences néfastes sur la santé, l'économie et la société, Covid-19 a également fourni l'occasion de mettre en évidence l'immense potentiel de la médecine traditionnelle africaine en tant qu'alternative valable pour faire face à une menace majeure pour la santé. La médecine traditionnelle africaine a joué un rôle déterminant dans le contrôle de la pandémie de Covid-19 sur le continent, en situation de couverture vaccinale extrêmement faible. Pour une utilisation optimale et durable de la médecine traditionnelle, nous recommandons fortement que les produits soient développés conformément aux normes de l'OMS, tout en tenant compte des questions de durabilité, de protection de l'environnement et de droit d'auteur entourant la recherche et le développement de médicaments à base de produits naturels.

Mots clés : Covid-19, Medicament Traditionnels Ameliorés, Standard OMS, Cameroun

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Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic started in December 2019 (Zhou *et al.*, 2020), where China notified the World Health Organization (WHO) of numerous cases of pneumonia of unknown cause in Wuhan (WHO, 2020a). The novel coronavirus outbreak was officially declared as a public health emergency of international concern on 30 January 2020 (WHO, 2020b). The outbreak spread in an unprecedented way to quickly invade all the world continents affecting 228 Countries and Territories around the world, with a total of 541 313 815 confirmed cases, and a death toll of 6 327 547 deaths: (42%) of the total cumulative cases in Europe, (30%) in Americas, (12%) in West-Pacific, (11%) in South-East Asia, (4%) in Eastern Mediterranean, and (2%) in Africa, as of June 26th, 2022 (WHO, 2022). At the emergence of the covid-19 in 2020, it was reasonably predicted the African continent would be one of the most affected, as a result of the fragile health systems, ill-prepared to deal with the pandemic (Bang et al., 2020; WHO, 2020c). Unaccountably, the impact of COVID-19 has been relatively less severe in Africa, compared to the global North (Titanji, 2021, Laurencin and McClinton, 2020). Still, the long term impacts of the pandemic on virtually every aspect of our society (health, economy, politics, security) are likely to be major (Africa CDC, 2021; Leke, 2021). In order to be able to mitigate the spread of this disease, countries adopted restrictive measures ranging from partial to total confinement (Tchinang, 2020). Strategies consisted essentially of (i) barrier and hygiene measures to stop the virus transmission (social distancing, hand washing, wearing of face masks, lockdowns and self-isolations etc.), and (ii) case identification and management (Titanji, 2021). However, the pandemic has caused profound disruptions to the functioning of societies and their health systems in resource-limited countries (Polsek *et al.,* 2022). As the scourge reached a planetary scale, there became a real psychosis, due to its rapid spread, the mode of contagion, and the absence of effective curative and preventive solutions. Almost 20 years ago, Savarino et al. hypothesized the possible usefulness of chloroquine and hydroxychloroquine in the treatment of SARS-CoV (Lasheras and Santabárbara, 2020). Several other studies have suggested genetic homologies between the SARS-COV-2 and malaria species. Using both experimental and predicted *in silico* approaches, Iesa *et al.* (2020) found possible shared immunodominant epitopes between SARS-CoV-2 and *Plasmodium falciparum* antigens. The authors concluded that these findings could suggest an explanation to the lowest number of COVID-19 infections and mortality rates exist in malaria-endemic regions compared to the rest of the world. It was also demonstrated that T cell epitopes of SARS-CoV-2 spike protein and conserved surface protein of *Plasmodium malariae* share sequence homology (Hassan *et al.*, 2021). With the Covid-19 pandemic, this postulate has prompted high interest and hope in antimarials repurposing as therapies against the new disease (Wang *et al.*, 2020; Gao et al., 2020; Colson *et al.*, 2020). In a continent where part of the population still has significant difficulties in accessing care, the prospect of treatment based on accessible, inexpensive and familiar medicines then appear as an opportunity and a blessing. This situation has led to the search for therapeutic solutions based on traditional medicine to deal with the pandemic in Africa. However, the global strategy for the fight against COVID-19, whether in the management or the prevention of the disease, has been almost exclusively based on evidence-based Allopathic (Western) Medicine practice, almost to the exclusion of African traditional medicine which is rather essentially in essence (Titanji, 2021). The proportions of patients relying on traditional remedies vary widely, depending on cultural and socioeconomic factors. In the case of malaria for instance, it is estimated that over 1200 plant species (of which over 200 identified for malaria in Cameroon) belonging to 160 families are used to treat malaria and other fevers and some of these natural products have proved to be quite effective (Titanji *et al.*, 2008; Zofou *et al.*, 2013). Medicinal plants play an important socio-economic role by fulfilling health-care needs and providing business opportunities and employment to the local people. During the past Ebola Virus Disease outbreak of 2014–

2016 in West Africa, several recipes of indigenous herbal therapies were equally reported in several countries affected (Balde *et al.*, 2016). However, issues regarding the safety, effectiveness, quality, availability, preservation and regulation of traditional and complementary medicine need to be addressed (WHO, 2013).

The aim of the present review work is to elaborate on the contribution of the local pharmacopoeia of African continent and Cameroon in particular, for the fight against covid-19; while emphasizing on the requirements and procedures for improving Traditional Herbal Medicines to WHO Standards, for safer and universal use.

A. Traditional Medicine in the Cameroon Health system

WHO estimates that about 80% of people globally rely on herbal medicines, traditional treatments, and traditional practitioners as the main source of health care, and sometimes the only source of care; because of their accessibility and affordability of these form of medicine which are also culturally acceptable and trusted by many people (WHO, 2013). WHO, with mission to help save lives and improve health, supports T&CM, through: (i) facilitating integration of T&CM into national health systems by helping Member States to develop their own national policies in this sector; (ii) producing guidelines for T&CM by developing and providing international standards, technical guidelines and methodologies for research into products, practices and practitioners; (iii) stimulating strategic research into T&CM by providing support for clinical research projects on its safety and effectiveness; (iv) advocating the rational use of T&CM through the promotion of its evidence-based use; and (v) mediating information on T&CM by acting as a clearing-house to facilitate information exchange.

The WHO policy is strongly endorsed and supported by Africa CDC and the African Union Commission for Social Affairs which have issued statements welcoming traditional medicines for the management of COVID-19, and proposed guidelines for protocol for Phase III clinical trials of herbal remedies (Yimer *et al.,* 2021). In Cameroon, T&CM play a key role in daily heath care. Local medicines are even preferred to modern medicines in ethnic groups such as Baka Pygmies in South Eastern Cameroon (Betti, 2004). There exist two types of traditional pharmacopoeia: the specialized pharmacopoeia which is practiced by traditional healers for difficult health problems, and the popular or general pharmacopoeia which is common knowledge in a given community and is used by individuals mostly for treating ordinary ailments such as fever, malaria and diarrheas. Traditional medicines are commonly sold in markets and public places or administered by healers in traditional clinics. TM is divided into three main categories:

- ✓ **Category 1**: Traditional medicines that are prepared by a traditional health practitioner for an individual patient with fresh or dried raw materials, with a short shelf life.
- ✓ **Category 2**: Traditional medicines currently used in the community that are prepared in advance and composed of crude raw plant materials.
- ✓ **Category 3**: Standardized plant extracts prepared in advance and supported by scientific research.
- ✓ **Category 4**: Isolated pure compound molecules from traditional medicines following scientific research.

At the level of the Ministry of Public Health, three technical departments and a Public Administrative Establishment play a role in the development of TM (Table 1).

The Institute of Medical Research and the Study of Medicinal Plants (IMPM) is a main stakeholder collaborating with the Ministry of Public Health for the promotion of TM. The structure participate in routine quality control activities while it remains very active in research and valorization of the local pharmacopoeia. Several organizations promote activities of traditional healers, and ensure good practices in the country. Local officials have the authority to allow or restrict the practice of traditional medicine in their administrative and/or health subdivisions, and

some traditional medicine practitioners are involved in Cameroon's primary health care program (Vasisht and Kumar, 2004). Whole plants or parts of them are prepared and administered as monoherbal or polyherbal oral decoction, steam baths, infusion or enema. Several research projects have been undertaken on local medicinal plants.

Table 1: Structures of the Ministry of Public Health in charge of TM in Cameroon

Structure	Role
The National Laboratory for Quality Control of Medicines and Expertise (LANACOME)	✓ Quality control of drugs, cosmetics, food products; biometrics and Improved Traditional Medicines.
The Health Care Organization and Technology Department (DOSTS)	✓ Monitoring and supervision of activities related to traditional social and health services; ✓ Development of collaboration between the social and health service providers and the health services.
Division of Operational Research in Health (DROS)	✓ Monitoring research on the use of improved traditional medicines, in conjunction with the Ministry in charge of research; ✓ Support for research on medicinal plants
Department of Pharmacy, Medicines and Laboratories (DPML)	✓ New Drug Registration, TM; ✓ Pharmacovigilence; ✓ Promote drug stewardship

Source: Kamga (2020)

B. From Traditional Remedies to Improved TM : Steps, requirements and challenges

Drug research and development (R&D) from natural products in its traditional approach, is generally a long and laborious process requiring substantial funding, good infrastructure, qualified personnel and an enabling political and institutional environment (Titanj *et al.*, 2017). The starting product, from a range of sources (plants, marine flora and microorganisms) may be chosen and screened at random or the source-materials may be selected based on previous knowledge (ethno-botanical or ethno-pharmacological surveys) of their use in communities. A wide range of technologies is available for the extraction of active components and essential oils from medicinal and aromatic plants. The choice depends on the nature of the source material, the nature of experimental techniques and models employed as well as cost feasibility and the suitability of the process to the particular context. Crude extracts with promising activity typically undergo bioassay-guided fractionation towards detection and isolation of potentially active pure ingredients. The use of ethno-botanic information to select plants for screening has proved to be a fruitful and cheaper approach for drug discovery. Once identified, active principles can be optimized by chemical synthesis to obtain more active products at affordable costs. The entire pool of molecules present in different parts of the plant under consideration can also be isolated and tested against different parasite types in the search for potentially active compounds.

However, the outcome of drug research and development, particularly from plant source also depends on a number of factors (Zofou *et al.*, 2014) which include (i) the relative abundance and widespread of the plant species; ii) the yield of the active ingredients, and least variability over plant sub/species or varieties if any, (iii) the possibility of mass production of the active ingredient by synthesis, for example; iv) the stability in the concentration of bioactive ingredients with genetic, climatic, edaphic and ecological changes; v) adequate analytical and production methods. Assurance of safety, quality, efficacy and affordability of

medicinal plants and herbal products is therefore a critical issue (Nika *et al.*, 2012). As defined by American Herbal Product Association (AHPA), standardization (applying to herbal preparations) refers to a body of information and control tools necessary to insure product material of reasonable consistency.[151,152] Protocols for standardization of herbal extracts include a proper identification of the plant species; physical parameters (organoleptic, viscosity, moisture, pH, hardness, etc.); chromatographic and spectroscopic evaluation of chemotypes (using UV, FTIR, HPTLC, HPLC, GCMS, LCMS, NMR) microbiological parameters (*Escherichia coli* and molds, aflatoxin); pesticide residue (DDT, BHC, toxaphene, aldrin) and heavy metal analysis (Mercury, Lead, Cadmium, Arsenic, Copper, Iron, Zinc). In addition of containing no or only sublethal among of toxic element, a good source of herbal medicine should be a widespread medicinal plant growing in different edaphic and climatic environments. The phytochemical composition, especially the content in active ingredients should remain in a very narrow range despite the diversity of habitats.

With regards to medicinal plants as a source of lead compounds, priority will be given to those with highest extraction yield, shorter lifespans like herbs and shrubs which can easily be cultivated. Lead compounds that can be synthesized cost-effectively are preferable.

C. Strategies and experimental models for Covid-19 Drug Discovery and development

SARS-CoV-2 is an enveloped single-stranded, positive-sensed RNA virus, with trimeric spike (S) proteins-mediated invasion mechanism through human plasma membrane angiotensin-converting enzyme 2 (hACE2) (Pandamooz et al., 2021; Zhou *et al.,* 2020). The past two decades have witnessed three major pandemics of coronavirus cause, namely the first severe acute respiratory syndrome (SARS), in the Guangdong province of China in 2002 (Drosten *et al.*, 2003), the Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia in 2012 (Zaki *et al.,* 2012), and the current Wuhan-originated Covid-19 pandemic. Strategies as well as experimental models for Covid-19 drug discovery and development have been extensively explored (Shyr *et al.*, 2020; Zhou *et al.*, 2021; Pandamooz *et al.*, 2022; Wang *et al.*, 2022).

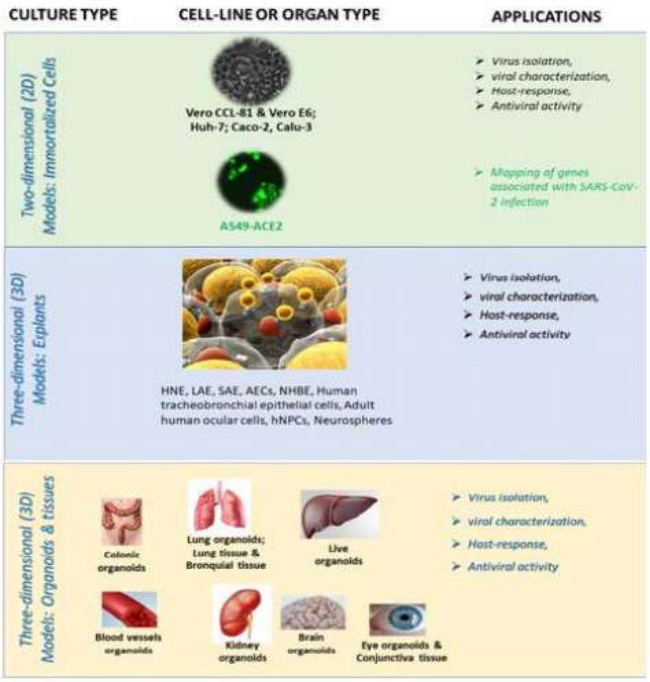

Figure 1: *In vitro* Experimental models for Covid-19 research (Adapted from Rosa *et al.* (2021).

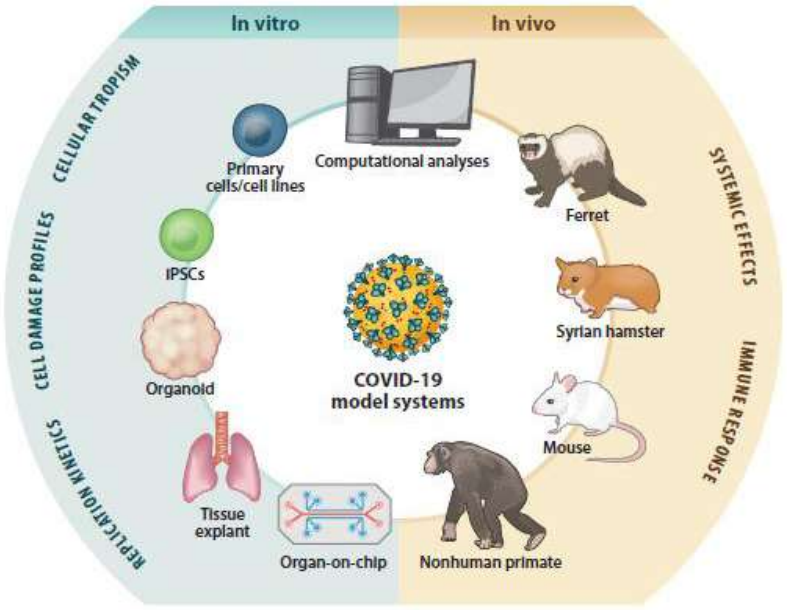

Figure 2: *In vivo* Experimental models for Covid-19 research (Adapted from Pandamooz *et al.,* 2022, and Rosa *et al.* (2021)

Exploiting the numerous functional similarities between SARS-CoV, SARS-CoV-2, and MERS-CoV, it was hypothesized that broad-spectrum anti-coronavirus drugs could also be useful against this new pandemic. This justified why drug repurposing has been successful right from the onset of the pandemic. Several groups have identified compounds with anti-SARS-CoV-2 activity using this strategy (Choy *et al.,* 2020; Jeon *et al.*, 2020; Wang et al., 2020).

Chakraborty (2021) reviewed the status of the treatment of COVID-19 through drug repurposing, including the lessons learned from the experience from using various therapeutic molecules to treat the COVID-19 patients like hydroxychloroquine, ritonavir/lopinavir, favipiravir, remdesivir, ivermectin, dexamethasone, camostatmesylate, tocilizumab, mavrilimumab, baricitinib, and interferons (IFN). Drug repurposing is a fast and cost-effective approach, though the predicted efficacy is not always obtained.

High-throughput drug repurposing screens has been implemented to accelerate the screening process. Several models have been designed for Covid-19, ranging from *in vitro*, *ex-vivo, and in-silico* through *in vivo*, each with advantages and limitations (Figure 1).

The choice of a model is dictated by the suggested mode of action of drug being investigated. For instance, potential immunomodulators would be tested using any of the following *in vitro* models: Primary cell culture (Human airway epithelium), iPSC-derived Cells (iPSC-derived lung and macrophage coculture), Organs-On-Chips (Intestine-on-a-chip), Tissue explant (Human lung tissue explants). While VeroE6 cells are used mostly for SARS-CoV-2 replication and isolation, Caco-2 cells (human epithelial colorectal adenocarcinoma), and Huh7 cells (hepatocellular carcinoma) are preferred for *in vitro* dug screening.

In vivo models are more versatile, but complementary. The mouse's small size and rapid breeding make it a suitable for rapid screening of antiviral drugs and vaccines, but this model lack appropriate ACE2 receptors, which does not make it a good substitute for human infections. Hamster for its own, is very susceptible to SARS-COV-2 infection and closely mimics disease stages. This is a great advantage for this animal as a perfect model for viral transmission and vaccine studies. However, it distends largely from human in pharmacokinetics. Nonhuman primates are the ideal model for both the disease pathogenesis,

vaccines and drug studies, though their use is highly limited by ethical and species protection issues. On July 4th, 2022, a total of 8164 clinical trials on Covid-19 vaccine and drug development have been registered in 150 countries (https://clinicaltrials.gov/ct2/covid_view, accessed on 04/07/2022). Of these registered trials, 2132 were on a total of 673 drugs being tested. Covid-19 treatment might include drugs with direct action on the virus (Monoclonal antibodies Bamlanivimab and Etesevimab; replication blocker Remdesivir and Molnupiravir), those acting indirectly through anti-inflammatory (Baricitinib, Dexamethasone), anti-oxidant (Vitamin C), immune-modulatory (Vitamin D3), anti-symptom (antipyretic, anti-cough, etc.) effects (Titanji, 2021).

D. Contribution of Traditional Medicine in the Response to Covid-19 in Cameroon and Africa

Faced with the meteoric spread of SARS-COV-2, coupled with the absence of any effective therapeutic or preventive solution, the whole world was panicked throughout 2020; and each society was doing its best to find a solution to this unprecedented situation. Thus, the oldest form of medicine (Traditional Medicine) wasn't long in coming, whether in China, India or Africa. Supported by some evidences of similarity/homology both at phenotype and genotype levels, the drug repurposing strategy quickly gained field. Thus traditional recipes known for any flu-like pathology or malaria became popular, especially in the African continent. This was particularly supported by the inflammatory and oxidative stress patterns of Covid-19; and more importantly, the encouraging results from the early in vitro and clinical trials with the famous antimalarial drug chloroquine / its derivative hydroxychloroquine in China, at the onset of the pandemic (Liu *et al.,* 2020; Chen *et al.,* 2021). The African continent witnessed an unprecedented infatuation of researchers, health practitioners, traditional healers and even religious to find therapeutic solutions or at least palliatives to this scourge (Tchinang, 2020). Fedoung *et al.* (2020), in a review work reported a total of 230 revealed as potential source of ingredients for the fight against covid-19. Thirty of these had been shown to contain confirmed anti-COVID-19 secondary metabolites, while 90 were reported for their traditional use in managing at least 3 common symptoms of COVID-19. Some of the reported plant species have immunostimulant activity, anti-inflammatory activity, antiviral properties or antimarial properties. Ebob et al. (2021) conducted a similar review work, focusing on natural products with inhibitory concentrations 50% below 10 μ M on SARS-COV-2. The authors identified a total of 42 compounds belonging to the alkaloid, flavonoid, terpenoid, phenolic, xanthone and saponin classes, for which they recommended further investigations in the light of developing new anti-covi-19 molecules. Tchinang (2021), Yimer *et al.* (2021), and Titanji (2021) extensively reviewed achievements in Cameroon and Africa in response to Covid-19. The most popular ones in Cameroon are the Adsak Covid/Elixir Covid, produced by the Archbishop of Douala, Mgr Samuel Kleda, Corocur powder by Euloge Yagnigni, Palubek's by Christine Bekono and Soudicov Plus by Imam Modibo (Titanji, 2021). Out of Cameroon, we can list the Covi-Organics (Arteminsia-based) of Madagascar; Apivirine (*Dichrostachys glomerata)* from Benin (Nabaloum, 2020); Fagaricine (Tea from Zanthoxylum heitzii) developed on Gabon (Mayombo 2020); Imunitum, Immu-Top, Secure and Biocire developed I Togo (Dia, 2020).

Concluding remarks

This review reveals that beside its multifaceted consequences on health, economy and the society, Covid-19 has also provided opportunity to highlight the immense potential of traditional medicine as a valid alternative for addressing major health threat. Despite some success stories of plant-based Improved Traditional Medicines in the management of the scourge, it is crucial to stick to WHO standards, while taking into consideration sustainability, environmental protection and copyright issues surrounding the natural product-based drug research and development.

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