

Harnessing Traditional Knowledge to Treat Existing and Emerging Infectious Diseases in Africa

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INTRODUCTION

Worldwide, infectious diseases, such as diarrheal diseases, human immunodeficiency virus (HIV), malaria, measles, pneumonia, and tuberculosis remain some of the major causes of human mortality and morbidity, even after the arrival of modern antimicrobial chemotherapy. Chemotherapeutic agents developed since World War II include drugs effective against bacteria, fungi, parasites, and viruses. Perhaps the most important antibacterial agents in clinical use remain antibiotics, many of which have been derived from natural sources. Natural sources have also yielded numerous substances with insecticidal, antimicrobial, and antiprotozoal potential. Many such compounds, including essential oils, are active against all these classes of organisms. They can be used internally (e.g., for protozoal infections, and those with antiviral polyphenolics for influenza

and colds), as well as externally for skin infections and infestations. In addition, intestinal worms have been treated with herbal materials such as wormwood.

A comprehensive study on natural products carried out between 1981 and 2002 has shown that of the existing 877 small molecules, 67% of new chemical entities are synthetic but the origin of over 16% could be traced to a pharmacophore derived from a natural source. Interestingly, 12% of these molecules have been modeled on a natural product inhibitor of a molecular target of interest or were designed to mimic an endogenous substrate or active site such as ATP. Therefore, from this logic, only 39% of the 877 molecules could be classified as being truly of synthetic origin. As for the anti-infectives (antimicrobial, antifungal, antiparasitic, and antiviral), almost 70% of the active molecules were derived from natural sources. Of those molecules used to treat cancer,

67% are in this category [1,2]. With increasing resistance being observed in various pathogens, there has been a renewed interest in “relooking at natural product as a source of leads” [3]. Hence, Nature has and will continue to play a lead role in the discovery of active natural products that have bearing on and shape drug discovery in the medium to long term [4,5].

Resistance toward existing antibiotics is developing [6] and increases in the death toll related to Methicillin-Resistant *Staphylococcus aureus* (MRSA) or antibiotic-resistant *Escherichia coli* have been reported recently [7,8]. Besides MRSA, other pathogens, such as *Candida albicans* and *Pseudomonas aeruginosa*, are posing an impending threat to human health [9]. MRSA infections affect approximately 94,360 individuals in the USA and are linked to around 18,650 deaths annually [10], even in well-regulated health systems like those prevailing in Europe.

Developing countries from Africa are not spared and will bear the brunt of this pandemic if proper and timely measures are not taken. It is also worth pointing out that the death toll from these infectious diseases is more than 11 million worldwide each year, with the majority of deaths occurring in many parts of Africa. Sub-Saharan countries are the worst hit and are finding it difficult to cope, with their limited infrastructure and resources [11,12].

THE BURDEN OF MULTIDRUG RESISTANCE AND EMERGING INFECTIOUS DISEASES

While existing infectious diseases are proving to be a challenge, newly emerging infections are also adding to the burden. These are attributed to mutations in the microorganisms that infect humans, and reemerging infections are also now known to be spreading at a high rate [13]. Examples of emerging infectious diseases (EIDs) in Africa include avian influenza, Ebola, monkeypox, Marburg, and,

more recently, chikungunya. Over and above the human tragedy, EIDs can have devastating economic effects on livestock and the populations dependent on them.

Moreover, multidrug resistance of existing infectious pathogens is currently hampering efforts to advance eradication of diseases. For instance, multidrug-resistant tuberculosis (MDR-TB) is becoming a life-threatening form of tuberculosis, affecting more than half a million people every year, that causes much higher mortality rates than drug-susceptible tuberculosis. MDR-TB is on the rise in some countries, yet only 3% of cases are being treated according to standards set by the WHO. If MDR-TB is not vigorously addressed, it stands to replace the mainly drug-susceptible strains that cause 95% of the world's tuberculosis today. Using surveillance data from the WHO and its partners generated since 1994, it is estimated that about 510,000 cases of MDR-TB occur every year, of which tens of thousands are classified as extensively drug-resistant tuberculosis (XDR-TB). In some countries, MDR-TB rates are rising, while in others they are falling. Among the world's 12 million cases of tuberculosis in 2010, the WHO estimates that 650,000 involved MDR-TB strains and it is projected that the treatment of MDR-TB is “extremely complicated, typically requiring 2 years of medication with toxic and expensive medicines, some of which are in constant short supply. Even with the best of care, only slightly more than 50 percent of these patients will be cured.” [14]. For most countries, the data are not yet good enough to predict trends and, according to Dr. Margaret Chan, director general of the WHO, antibiotic resistance could bring about “the end of modern medicine as we know it” [15,16].

EIDs also present a real challenge to research scientists, who are actively looking for substitute drugs to cope with the growing resistance to antibiotics. Halting the trend of increased emerging and resistant infectious diseases will require a multipronged approach that includes

the development of new drugs. In this context, traditional herbal remedies from the tropics, in particular those from the African continent, present an untapped potential. Indeed, using plants as the inspiration for new drugs provides an infusion of novel compounds or substances to combat infectious diseases. To this effect, bioprospection from tropical flora (both medicinal and nonmedicinal) presents a useful route toward the search for new molecules and remedies.

TRADITIONAL MEDICINES AS AN ALTERNATIVE SOURCE OF NOVEL PHARMACOPHORES

The WHO reported that 80% of the emerging world's population relies on traditional medicine for therapy. Since 2000, the developed world has also been witnessing an ascending trend in the utilization of complementary and alternative medicines (CAMs). While 90% of the population in Ethiopia use herbal remedies for their primary health care, surveys carried out in developed countries like Canada and Germany showed that at least 70% of their population have tried CAMs at least once. It is likely that the profound knowledge of herbal remedies in traditional cultures, developed through trial and error over many centuries, along with the most important cures have been passed on orally from one generation to another. Modern allopathic medicine is firmly anchored in this ancient medicine and it is more than likely that important remedies will be found in traditional remedies and will be commercialized in the future. These successes will rest on leads discovered from traditional knowledge and related expertise.

The composition of medicinal plants is known to be very diverse and to consist of different chemical substances that can act individually, additively or synergistically to improve health conditions. By way of example, one plant can

contain anti-inflammatory compounds that bring down swelling or reduce pain, as well as a bitter substance that stimulates digestion. Phenolic compounds are known to act as antioxidants and venotonics, while tannins classically act as antimicrobial agents (or natural antibiotics). In addition, compounds that induce diuresis would promote the elimination of waste products and other toxins. Further, alkaloids are known to be mood enhancers and can promote a sense of wellbeing.

TRADITIONAL AFRICAN MEDICINE

Globally, African herbal medicine is perhaps the oldest and the most diverse form of all medicine systems. The African continent is rich in biologic and cultural diversity and is known as the cradle of mankind. Its cultural diversity is marked in geographic terms, and regional differences affect healing practices. The African system of medicine has been transmitted orally and its documentation remains a challenge, especially in the light of rapid biodiversity loss coupled with the loss of habitats through anthropogenic activities. The African continent has one of the highest rates of deforestation in the world. At the same time, the paradox is that it is also a continent with a high rate of endemism. The island of Madagascar, for example, tops the list, with 82% of its flora being endemic. African traditional medicine is also very varied and holistic, involving both the body and the mind. The traditional healer normally diagnoses and treats the underlying psychologic basis of an illness before prescribing medicines to treat the symptoms.

The recent publication of the *African Herbal Pharmacopoeia* has shed light on the potential of the African flora on various diseases [17]. This document brings together important medicinal plants from all parts of the continent: *Acacia senegal* (gum arabic) and *Aloe vera* from

North Africa; *Aloe ferox* (Cape aloe), *Agathosma betulina* (buchu), *Aspalathus linearis* (rooibos tea), *Harpagophytum procumbens* (Devil's claw), and *Hypoxis hemerocallidea* (African potato) from Southern Africa; *Boswellia sacra* (Frankincense), *Catha edulis* (khat), and *Commiphora myrrha* (myrrh) from Eastern Africa; and *Artemisia afra* (African wormwood), *Hibiscus sabdariffa* (Hibiscus, Roselle), and *Prunus africana* (African cherry) from Central and West Africa. The island of Madagascar has contributed *Catharanthus roseus* (rosy periwinkle). This country has the potential to contribute even more by virtue of its unique biodiversity.

SUB-SAHARAN AFRICAN BIODIVERSITY IN THE FIGHT AGAINST INFECTIOUS DISEASES

Malaria

If there was a disease that illustrated the troubled medical history of humans, it would no doubt be malaria. It kills millions of people annually throughout the world, and the majority of victims are children [18]. More than 10% of the US overseas troops in 1943 acquired malaria, and it has been reported that Alexander the Great died of it in June 2323 BC. Untreated, malaria may kill about 1% of those infected, and the survivors are prone to relapse. It is generally accepted nowadays as the most deadly parasitic disease in the world. It was in the eighteenth century that Dr. Francisco Torti coined the name *malaria* by combining the Italian words for *bad* (*mala*) and *air* (*aria*). At the time, it was generally believed that this disease was caused by the unhealthy air found around marshy areas. It was only later, toward the middle eighteenth century, that the connection was made between the transmission of this disease and the mosquito vector. This resulted in a need for mosquito control, leading to the eventual draining of marshes throughout

parts of the world where this disease was prevalent. Dichlorodiphenyltrichloroethane (or DDT), in spite of its bad reputation, has been perhaps the only insecticide to have saved millions of lives.

It was reported that as far back as the fifteenth century, doctors were dreaming of a plant-based medicine against this scourge. They first identified one such plant in Lima, Peru, the capital of New Spain. It was reported that the recovery was very high for a place where malaria is reported to be endemic. Jesuit priests observed that the local Indian population was not affected by this disease. It was later discovered that the secret of their health resided in the bark of a tree, which upon mixing with water, cured the associated fevers. The locals called the tree the *quina* or *fever bark tree*. By the end of the seventeenth century, quinine powder was the standard treatment for malaria. Over that particular period in history, Spain controlled much of the trade, as it had exclusive mandates in Bolivia and Peru. The demand for the quina was so great that soon there were not enough trees to assure supplies, and collectors of this precious remedy had to go further into the forest to find more trees. Many of them never returned, as they got lost and died either from dysentery or from the darts of Jivaro Indians. By the middle of the eighteenth century, French botanists had confirmed that there were in fact four species to this tree genus. Linnaeus confirmed this information and gave the name *Cinchona* to this tree in honor of the Viceroy of Peru, who lived between 1628 and 1639 [18,19].

The recent WHO Malaria Report (2011) [20] estimates that 3.3 billion people were at risk of malaria in 2010, although, of all geographical regions, those populations living in sub-Saharan Africa have the highest risk of acquiring malaria: among 216 million episodes of malaria in 2010, approximately 81% (or 174 million cases) occurred in the African region; and of an estimated 655,000 malaria deaths in 2010,

91% were from Africa. Resurgent vector-borne diseases result in a high burden of disease, estimated as approximately 56 million disability-adjusted life years [21]. Today, malaria has become a critical and widespread disease; one of the main reasons for this is that the efficacy of antimalarial drugs, including chloroquine, has been reduced by the spread of drug-resistant strains. This loss in efficacy is a major barrier to the effective treatment of malaria and has posed an urgent challenge for the discovery new antimalarial drugs. Malaria is caused by four species of the genus *Plasmodium*, namely *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Almost all fatalities are due to *P. falciparum* infections and, therefore, it is the most important species, but *P. vivax* also causes significant morbidity. This shocking reality is largely due to the emergence of drug-resistant strains of *P. falciparum*. In the early days, quinine was the curative agent for malaria and, subsequently, quinoline antimalarials and related aryl alcohols were developed based on the quinine prototype. This led to the emergence of drugs such as chloroquine and mefloquine.

With the rise of parasite resistance to these antimalarials, it became necessary to search for other synthetic and natural product-based agents. Another plant long used in the treatment of fevers in Chinese traditional medicine was therefore considered. The idea of investigating the antimalarial activity of wormwood came from Chinese herbal medicine, as this herb was first prescribed for fevers by the Chinese physician Li Shi-zen in 1527 [22].

Artemisia Species (Asteraceae)

Artemisia annua is a medicinal plant whose use has long been reported in China, where it is locally known as qinghao. It is now grown commercially in many African countries. Also known as Sweet wormwood, *A. annua* yields artemisinin and the derivatives of this compound are potent antimalarial drugs. Artemisinin is an endoperoxide sesquiterpene lactone

that is effective against multidrug-resistant malaria and is also known to act on *P. falciparum*, the *Plasmodium* species that causes cerebral malaria. The clinical efficacy of this drug and its derivatives is demonstrated by an immediate and rapid reduction of parasitemia following treatment [23]. Since the WHO recommended the use of artemisinin-based combination therapies for malaria in 2001, a number of other forms of *A. annua* L. have appeared as antimalarial remedies, including tea bags made from the plant's leaves.

Artemisinin was first isolated in 1972 and has served as prototype for many semisynthetic versions such as arteether and artemether. These compounds have increased solubility in vaccines and have improved antimalarial activities. However, although these synthetic and semisynthetic molecules are being tested widely, malaria remains a big threat to poorer countries, where these modern antimalarial drugs are not available to the general public. In these poorer countries, randomized trials have been performed to assess the efficacy of a traditional herbal tea made from the leaves of *A. annua*, especially for the treatment of uncomplicated malaria. It was observed that after 7 days of medication, cure rates were high (74%). Unfortunately, trials also confirmed that recrudescence was high and, hence, monotherapy with *A. annua* could not be recommended as a potential alternative treatment for this disease [24,25]. A combination of these treatments, however, was recommended [26].

Although Asian *A. annua* is now being grown on the African continent, *A. afra*, commonly referred to as African wormwood, is more commonly used in traditional medicine against infections and malarial fever. *A. afra* essential oil is exceptionally variable and its composition depends on its geographical origin. For example, Ethiopian oil yields artemisyl acetate and yomogi alcohol as the dominant constituents, while those of South African origin contain 1,8-cineole, α - and β -thujone, as well as camphor

and sesquiterpenoids. Recent *in vitro* and *in vivo* studies have confirmed the pharmacologic efficacy of these plant extracts [17]. The next question to address is how quickly malaria will evolve resistance to artemisinin. Recent observations in Southeast Asia and sub-Saharan Africa have been worrying. For instance, it was reported that malarial parasites from sub-Saharan Africa may be acquiring mutations that make them resistant to artemisinin, the backbone of new antimalarial therapy. A team of researchers from Canada and the United Kingdom studied parasites obtained from travelers who returned to Canada with malaria after trips abroad (11 from Africa, including Angola, Cameroon, Congo, Ghana, Kenya, Liberia, Nigeria, and Tanzania) between April 2008 and January 2011. They found that 11 of the 28 parasites grown in the laboratory had a mutation that made them resistant to artemether. It is also reported that although parasites are showing drug resistance in malaria patients in Southeast Asia, the same strains are not being identified as resistant in laboratory studies, suggesting that the relationship between laboratory studies and patient treatment is not direct. It is therefore suggested that the spread of resistance may be exacerbated by the poor quality of antimalarials, which only kill the weaker parasites and allow the fittest to survive [27–30].

***Strychnos myrtoides* (Loganiaceae)**

The reemergence of malaria in the central highlands of Madagascar in the 1980s, coupled with the lack of inappropriate drugs, compelled the indigenous people to explore traditional herbal remedies. A group of plants showing promising activity are *Strychnos* spp. *Strychnos* spp. are regularly used in the local Malagasy Pharmacopoeia and also on mainland Africa. Their roots are used to treat constipation, coughs, and toothache, as well as epilepsy. The aerial parts of these plants are used against malarial fever [31]. In Madagascar, there is a reported prevalence of quinine-resistant

P. falciparum and attention is increasingly being focused on alternative medicinal plants that can treat drug-resistant malaria. Investigations on several plants have led to the isolation of crude alkaloids from the leaves of *S. myrtoides*. These alkaloids have been used locally as adjuvant to chloroquine. When combined with chloroquine at doses less than the IC₅₀, these molecules were shown to markedly enhance the effectiveness of synthetic drugs against chloroquine-resistant *P. falciparum* *in vitro*. They also enhanced chloroquine activity against a resistant strain of *P. yoelii* *in vivo*. By counter-current distribution separation of the crude alkaloid extract, two major bioactive constituents, strychnobrasiline and malagashanine, were isolated from this plant, along with four minor alkaloids [32]. Malagashanine was identified as the parent compound of a new subtype of *Strychnos* alkaloids, the C-21, Nb-secocuran indole alkaloids, which had previously been isolated from Malagasy *Strychnos* [33,34]. *In vitro*, both strychnobrasiline and malagashanine are devoid of both intrinsic antimalarial activity and cytotoxic effects, but exhibit significant chloroquine-potentiating activities. Tests performed *in vivo*, on the other hand, showed that these extracts exhibited cytotoxicity and significant chloroquine-potentiating activity, which would justify the empirical use of *S. myrtoides* (10 mg/kg conferred a 5% suppression of the parasitemia) [34].

Until now, an infusion of the stem bark of *S. myrtoides* in association with chloroquine has been successfully evaluated within a clinical setting. The final aim is to develop a purified standardized extract for use in clinical trials, with a view to developing an efficient and inexpensive drug to combat chloroquine-resistant malaria.

***Nauclea latifolia* (Rubiaceae)**

Nauclea latifolia is a savanna shrub commonly found in the Burkina Faso, Democratic Republic of the Congo, Gambia, and the Republic of

Benin, among others. Its medicinal uses are as a tonic and fever medicine; a chewing stick for treating toothaches, dental caries, and septic mouth, and for treating diarrhea, dysentery, and malaria. In most parts of West Africa, the bark is used against fever and malaria; hence, it has been described as *African quinine*. It is sometimes used in combination with *Khaya senegalensis*. Its key constituents are glycoalkaloids, indole-quinolizidine alkaloids, and saponins. Several indoloquinolizidine alkaloids were isolated from the root and include, among others, nauclefidine and nauclefine. Root and stem aqueous extracts have been found to be active against *P. falciparum* (FcB1 strain) *in vitro*, mainly at the end of the erythrocytic cycle (after 32–48 h). Nonetheless, a comparative randomized clinical trial using standardized extracts of the roots has been tested against symptomatic, but uncomplicated malaria in human volunteers in Abuja, Nigeria. The results showed that the standardized extract was efficacious against uncomplicated malaria: parasite clearance was better than with chloroquine and there were no serious side effects on organs or tissues [17]. Additionally, studies have shown that the root has antibacterial activity against Gram-positive and Gram-negative bacteria, as well as antifungal activity. It is most effective against *Corynebacterium diphtheriae*, *Neisseria* spp., *P. aeruginosa*, *Salmonella* spp., *Streptobacillus* spp., *Streptococcus* spp. [35,36].

Cryptolepis sanguinolenta (Asclepiadaceae)

This plant, commonly known as Ghana quinine, is a thin-stemmed twining and scrambling shrub. Its dried roots are commonly used in West and Central Africa to treat hepatitis, while the entire plant is used to treat malaria. The major alkaloid isolated from this plant is cryptolepine, but it has been reported that other alkaloids present in the plant are responsible for its biologic/pharmacologic activity. Measurement of its antiparasitic activity by ³H-hypoxanthine incorporation into the malaria

parasite indicates that the hydrochloride and hydroxy derivatives, as well as neocryptolepine, are more active than quindoline. *In vitro* results have proved encouraging, with IC₅₀ values of 47, 42, and 54 μ M, compared to values of 2.3, 72, and 68 μ M for chloroquine. Cryptolepine was the most effective, with IC₅₀ values of 27, 33, and 41 μ M for D6-chloroquine-sensitive, K-1 chloroquine-resistant, and W-2 chloroquine-resistant strains, respectively. The WHO carried out *in vivo* studies to demonstrate the clinical efficacy of the product converted into a tea-bag formulation—Phyto-Laria. Over a 7-day period, the mean parasite clearance time was 82.3 h. The overall cure rate was 93.5%, with only two cases of recrudescence on days 21 and 28. On the evidence of fever clearance and disappearance of parasitemia by day 7, according to WHO criteria, this tea-bag formulation was deemed to be effective in the treatment of acute uncomplicated malaria [37].

Quillaja saponaria (Soap bark tree; Rosaceae)

Quillaja saponaria is a South American tree reported to contain triterpenoid saponins [38]. These ingredients have been used for an experimental malaria vaccine [39]. Partial purification of the crude extract yielded QuilA, which has since been renamed Stimulon. Stimulon works as an adjuvant, i.e., a pharmacologic additive that improves the effectiveness of a vaccine by stimulating the production of antibodies [39].

Plants and Acquired Immunodeficiency Syndrome

Across the world millions of people have been and continue to be infected by HIV, the pathogen directly responsible for acquired immunodeficiency syndrome (AIDS). AIDS is a complex array of disorders resulting from the breakdown of the immune system. Globally, AIDS-related diseases remain a leading cause of death. A person infected with HIV becomes

highly susceptible to rare forms of cancer and to infections, often from opportunistic pathogens. HIV uses cells of the immune system (helper T cells and macrophages) as sites for reproduction. There, multiple copies of the viral genetic material (RNA) are made and packaged into new viral particles, ready for dispersal into new hosts. Thus, more cells of the host's immune system are killed or damaged with subsequent rounds of infection, in which millions of viral particles are produced every day. Despite the production of antibodies and helper T cells that normally fight disease, eventually the virus prevails and signs of infections and cancer associated with AIDS start to appear. To date, there is no known cure or vaccine against HIV and drugs that can slow the progression of viral infection or halt the onset of AIDS are scarce.

As early as 1989, the WHO had already voiced the need to evaluate ethnomedicines and other natural products for the management of HIV/AIDS: "In this context, there is need to evaluate those elements of traditional medicine, particularly medicinal plants and other natural products that might yield effective and affordable therapeutic agents. This will require a systematic approach," stated a memorandum of the WHO [40]. Plants and other natural products comprise a large repertoire from which to isolate novel anti-HIV compounds. Increasingly, new compounds from natural sources are being reported daily. Currently, around 55 plant families, containing 95 plant species, and other natural products have been found to contain anti-HIV active compounds, including diterpenes, triterpenes, biflavonoids, coumarins, caffeic acid tetramers, curcumins, hypericin, gallotannins, galloylquinic acids, limonoids, and michellamines. These active compounds can inhibit various steps in the HIV life cycle [41]. However, many remain unproven and others have so far only shown promise in *in vitro* studies. Secondary metabolites will continue to play a significant role in combating viral

infections, including AIDS infections, that result from a compromised immune system. It has been estimated that over 36,000 extracts have been tested by the American National Cancer Institute and 10% have been reported to exhibit anti-HIV properties [22].

***Calophyllum* Species (*Garcinia* family; *Clusiaceae/Guttiferae*)**

One of the most promising compounds against AIDS is been reported to be produced by a Malaysian tree that is a member of the *Garcinia* family (*Clusiaceae* or *Guttiferae*). This tree is valued both for its wood and resin. A thorough investigation of African species of the *Garcinia* family is warranted in the quest for novel anti-HIV compounds. Research into the Malaysian species showed that the latex of *Calophyllum lanigerum* and related species, such as *C. teysmannii*, manifests significant anti-HIV activity. The active constituent was found to be (–)-calanolide B, which could be isolated to provide yields of 20–30%. Of the eight compounds been isolated from *C. lanigerum*, calanolide A has shown anti-HIV activity; moreover, *C. teysmannii* has yielded calanolide B, which was found to be slightly less active than (+)-calanolide A, but has the advantage of being readily available from latex, which can be tapped in a sustainable manner by making small slash wounds in the bark of mature trees. Calanolide A is a type of coumarin and is now being tested in clinical trials. These drugs are being developed by Sarawak MediChem Pharmaceuticals, a joint venture company formed between the Sarawak State Government and MediChem Research, Inc.: (+)-Calanolide A (which has been synthesized by MediChem chemists) is currently in Phase II clinical trials, while (–)-calanolide B is in preclinical development. Both these calanolides can also be isolated from another *Calophyllum* species, specifically from the leaves of *C. brasiliensis* [42], and exhibit more or less the same pattern of activity. Eventually, these compounds may form part of the

antiviral ingredients included in an AIDS *cocktail* to slow the rate of AIDS progression and extend the lives of HIV-infected patients.

Another potential anti-HIV drug originating in Africa comes from the *Ancistrocladus* spp. of woody vines. Three new atropisomeric naphthylisoquinoline alkaloid dimers, michellamines A, B, and C, have been isolated from a newly described species of tropical liana, *A. korupensis*, found in the rainforests of Cameroon. These compounds are capable of completely inhibiting the cytopathic effects of HIV-1 and HIV-2 on human lymphoblastoid target cells *in vitro* [3]. Crude extracts from this plant have yielded michellamine B, a new alkaloid that has been shown to have activity against HIV in initial trials. Based on the observed activity and the efficient synthesis of the di-acetate salt, the National Cancer Institute (NCI) of the United States committed michellamine B to advanced preclinical development, but continuous infusion studies in dogs indicated that effective anti-HIV concentrations *in vivo* could only be achieved at close to neurotoxic dose levels. Thus, despite showing *in vitro* activity against an impressive range of HIV-1 and HIV-2 strains, the difference between the toxic dose level and the level anticipated to be required for effective antiviral activity was small, and NCI decided to discontinue further studies aimed at clinical development. However, the discovery of novel antimalarial agents, the korupensamines, from the same species [43], holds further promise.

***Sutherlandia frutescens* (Fabaceae)**

Sutherlandia frutescens is also known as cancer bush in South African and the southern African region. It is mainly used locally as a bitter tonic and an adaptogen.

The herb is known to be exceptionally variable and contains a large number of triterpenoid saponins. L-canavanine has been adopted as the marker molecule because it is a potent L-arginine antagonist with documented anticancer

and antiviral activities, including activity against the influenza virus and retroviruses. Recent observations have shown that significant clinical benefits can be obtained in the treatment of wasting in cancer and AIDS, which is supported by a US patent. Convergent clinical observations by health professionals and community workers suggest that daily treatment with *Sutherlandia* can improve appetite, facilitate weight gain, and improve CD4 counts in HIV-positive patients. However, these observations need to be verified by a controlled clinical study [22].

***Catharanthus roseus* (Rosy Periwinkle; Apocynaceae)**

Patients suffering from AIDS usually find themselves at risk of a range of diseases, including cancers, that would normally be controlled by the immune system. *Catharanthus roseus* has given medicine two very important anticancer drugs. One of these, a semisynthetic version of the anticancer alkaloid, vinorelbine, is known to disrupt the spindle fibers responsible for separating chromosomes during mitosis. It is effective at lower concentrations and has fewer side effects than alkaloids derived directly from the plant material. This new drug could also be useful in combating Kaposi sarcoma, a rare skin cancer usually associated with AIDS [22].

Chikungunya Virus

Chikungunya virus (CHIKV) is an arbovirus belonging to the family Togaviridae and the genus *Alphavirus*, which can be further classified into encephalitic and arthritic viruses. Of the 29 viruses belonging to the genus *Alphavirus*, six are arthritic viruses: CHIKV, Mayaro virus, o'nyong-nyong virus, Ross River virus, Semliki Forest virus, and Sindbis virus. Examples of encephalitic viruses are the western equine encephalitis and Venezuelan equine encephalitis viruses. A recent outbreak of Chikungunya

fever in the islands of the Indian Ocean has drawn attention to CHIKV, which was first identified in the 1950s in Africa. Intriguingly, it was initially classified as a neglected tropical disease, and it was only the sheer magnitude of the 2005–2007 CHIKV outbreaks that brought this virus to the attention of both the scientific community and the general public [42]. CHIKV has since then been associated with the urban *Aedes aegypti* mosquito (possibly supplemented by *Aedes albopictus*) in an epidemiologic cycle resembling that of dengue and characterized by the absence of an animal reservoir, direct human-to-human transmission by urban mosquitoes, and the potential for major epidemics [44,45]. *A. albopictus* is considered to be the vector in Reunion Island and other islands of the Indian Ocean.

To date, neither a vaccine nor a selective antiviral drug is available for the prevention or treatment of this debilitating viral infection, and treatment is mainly supportive. The majority of cases are relatively mild, although more significant sequelae are now known. Thus, an antiviral treatment is most useful for prophylaxis in vulnerable groups, such as the immunocompromised, and for management of severe cases [46,47]. Currently, chloroquine use is not justified as there is no conclusive evidence for its effectiveness. The antiviral effects of chloroquine were first described in 1969. Subsequently, in the early 1980s, it was shown to have an inhibitory effect against replication of the Sindbis and Semliki Forest viruses. Recent *in vitro* experiments using chloroquine have led to a successful reduction in CHIKV growth, and use of chloroquine phosphate solution has been shown to provide relief to patients. Chloroquine is active in cell culture and may alleviate the symptoms of arthritis by acting as an anti-inflammatory agent, although this latter activity is still under investigation. However, in a 2006 double-blind, placebo-controlled trial with 54 participants, no statistical difference in the mean duration of febrile arthralgia between

the placebo and chloroquine group was found [46,47].

Currently, there is therefore a need to identify new, potential drugs and many investigators have turned toward indigenous biodiversity for this. Interestingly, several Indian Ocean islands (Madagascar, Mauritius, and Reunion Island) have combined forces under an umbrella project—PHYTOCHICK—to combat this emerging virus threat via selecting natural drug candidates from locally available medicinal plants. So far, a number of promising leads have been discovered, and currently several attempts at bioassay-guided purification/fractionation of pure substances are underway and have yielded promising preliminary results. Concomitantly, enzyme assays are being developed to evaluate and provide a detailed characterization of the selective inhibitory effects of these phytocompounds. Overall, more than 1554 crude and filtered extracts and 22 pure compounds have been evaluated for cytotoxicity and evaluation against CHIKV. A total of 13 and 8 hit extracts were recorded for the Madagascar and La Reunion partners, respectively. Interestingly, 12 extracts have proven to be potent (i.e., providing a superhit against CHIKV) from Mauritius; these belong to the Celastraceae, Ebenaceae, Meliaceae, Rubiaceae, Sapindaceae, Sapotaceae, and Sterculiaceae families. Additionally, five plants from Mauritius were initially selected for further fractionation, phytochemical analysis, and anti-CHIKV evaluation. Promising leads have been found *in vitro* from four of these fractions; they have shown maximum inhibition of 88.8% at 20 µg/mL; 3.9% at 4 µg/mL; 100% at 20 µg/mL, and 95.3% at 20 µg/mL against the CHIKV virus, respectively.

CONCLUSIONS AND FUTURE PERSPECTIVES

Undeniably, drugs resistance has created resurgence and insurgence of a panoply of

infectious diseases, mainly CHIKV, HIV, and malaria. The major victims for these killers are developing countries with the poorest resources, such as African and Asian countries. Many investigators now strongly believe that studying traditional medicines may offer new template molecules to combat these diseases. Evaluating plants from the traditional African system of medicine can provide us with clues about how these plants can be used in the treatment and management of diseases. Many of the plants presented in this chapter show very promising activity as antimicrobial agents, thus warranting their further investigation. Nevertheless, the discovery of compounds with antimicrobial activities from traditional medicinal plant remedies remains a challenging task. Indeed, to be successful in such an endeavor, more highly reproducible and robust innovative bioassays are needed as our understanding of the multifactorial pathogenicity of microbial infection evolves. Therefore, it is of the utmost importance that investigators should devise new automated bioassays, with a special emphasis on high through-put procedures, for screening and processing data from a large number of phytochemicals within shorter time periods. Additionally, these procedures should be able to rule out false-positive hits and incorporate dereplication methods to remove duplicate compounds. The ultimate goal will be to establish structure-activity phytochemical libraries to boost new antimicrobial drug discovery.

On the other hand, one of the main constraints to the growth of a modern African phytomedicine industry has been identified as a lack of proper validation of traditional knowledge and of technical specifications and quality control standards. This makes it extremely difficult for buyers, whether national or international, to evaluate the safety and efficacy of plants and extracts, or to compare batches of products from different places or from year to year. This stands in marked contrast to Europe and Asia, where traditional methods and

formulations are recorded and evaluated at both the local and national levels. This could explain why the level of trade in Asia and Europe is higher than in Africa. Other issues that need to be addressed are those of Access and Benefit Sharing following the Nagoya Protocol. Local laws need to be TRIPS compliant if trade is to increase and, at the same time, issues of sustainable development need to be addressed. Nonetheless, despite the continuous, comprehensive, and mechanism-orientated evaluation of medicinal plants worldwide, there is still a dearth of literature since 2000 from investigations addressing procedures to be adopted for quality assurance, authentication, and standardization of crude medicinal plant products. Finally, above and beyond simple *in vitro* and *in vivo* assays, randomized, controlled trials must be carried out and reported for each claim and the data amassed should be provided to traditional healers.

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