JJBS

Jordan Journal of Biological Sciences

Volume 6, Number 2, June .2013
ISSN 1995-6673
Pages 77 - 84

African Flora as Potential Sources of Medicinal Plants: Towards the Chemotherapy of Major Parasitic and Other Infectious Diseases- A Review

Ameenah Gurib-Fakim[1,*] and Mohamad F. Mahomoodally[2]

[1]*Centre for Phytotherapy Research, 7th Floor, Cybertower 2, Ebene;*

[2]*Department of Health Sciences, Faculty of Science, University of Mauritius, Réduit, Mauritius*

Received: December 6, 2012; accepted January 21, 2013

Abstract

Parasitic diseases, especially those defined as neglected diseases by the WHO, remain a major public health predicament, which affects hundreds of millions of people especially in developing countries. Furthermore, infectious diseases such as HIV, malaria, tuberculosis, diarrhoeal diseases, pneumonia, leishmania and human African trypanosomiasis are responsible for one in two deaths in developing countries, where poverty, limited access to health care, drug resistance and a changing environment make populations particularly vulnerable. As a consequence, herbal medicines have attracted much attention as potential therapeutic agents in the prevention and/or management of parasitic and infectious diseases, as they can yield potential leads to address emerging infections and resistance. Indeed, the use of medicinal plants in the treatment and management of human and animal diseases has long been practiced before the advent of chemotherapy. The present review has endeavoured to provide an overview of the potential of medicinal plants, particularly, those from the African biodiversity to target three common parasitic and infectious diseases, namely malaria, leishmania and human African trypanosomiasis that have plagued humans since time immemorial.

Keywords: Medicinal Plants, Chemotherapy, Leishmania, Human African Trypanosomiasis, Malaria

1. Introduction

It is generally recognized that plants have formed the basis of sophisticated traditional medicine systems that have existed over millennia. Herbal medical products form part of systems of knowledge and practice that has been transmitted over centuries and is evolving fast. There is also no doubt that human beings rely on them directly or indirectly either as alternatives to mainstream medication or as isolated molecules that are derived from medicinal plants. Traditions like Chinese, Ayurvedic, Kampo, Arabic, European Unani, Jamu etc. are all good examples.

In the Western world, the Greeks have contributed substantially to the rational development of the use of herbal medicines. Theophrastus, in his *History of Plants*, dealt with the medicinal qualities of herbs, and noted the ability to change their characteristics through cultivation. Dioscorides had started recording the use of medicinal plants during his travels with the Roman armies. Galen, who practiced and taught pharmacy and medicine in Rome, published several books and he is well known for his complex formulas used in compounding drugs sometimes containing dozens of ingredients ("galenicals") (Heinrich *et al.*, 2004).

During the period 5-12th century, the remains of this western knowledge were preserved in monasteries. However, it was the Arabs who were finally responsible for the preservation of much of the Greco-Roman expertise, and for expanding it to include the use of their own resources, together with Chinese and Indian herbs unknown to the Greco-Roman world (Bashar *et al.*, 2008).

The Arabs were the first to establish privately owned drug stores in the 8th century, and it was Avicenna, the Persian physician and scientist who had contributed much to the sciences of pharmacy and medicine through works such as *Canon Medicinae*, which is regarded as "the final codification of all Greco-Roman medicine" (Bashar *et al.*, 2005)

Nowadays, plant-based systems of medicine continue to play an essential role in health care. The World Health Organization has estimated that approximately 80 % of the world's inhabitants rely mainly on traditional medicines for their primary health care (Anon, 2008).

* Corresponding author. e-mail: afakim@cephyr-recherche.com.

Plant products also play an important role in the health care systems of the remaining 20 % of the population residing mainly in the developed countries. It has been estimated that in the United States from 1959 to 1980, about 25 % of prescriptions contained plant extracts or active principles derived from higher plants, and at least 119 chemical substances have been derived from 90 plant species. Of the 119 drugs, 74 % were discovered as a result of chemical studies directed at isolating the active substances from plants used in traditional medicine. In addition, the use of so-called complementary or alternative herbal products has expanded in recent years (Cragg and Newman, 2007).

Whilst it is often acknowledged that traditional medicine works, there still exists gap in the scientific study of the complex products from such traditions. Such is the challenge that faces ethnopharmacology even though it is increasingly being acknowledged that many types of diseases, including such common ones as vector-borne diseases: diarrhea or tuberculosis are still commonly treated and/or managed with herbal medicines.

There is also a growing use of plants to manage or treat HIV/AIDS or other emerging or fast spreading diseases (like viral respiratory diseases). Novel treatment strategies are needed for all diseases and in recent years, herbal medicines from such traditions have received particular attention in the management (prevention or treatment) of chronic diseases like diabetes, chronic disorders and many forms of cancer.

In spite of the availability of antibiotics and vaccines, parasitic and infectious diseases still pose serious challenge in developing countries. Today, we are further away from controlling parasitic diseases than we were 30 years ago (Coker *et al.*, 2008; Nunkoo and Mahomoodally, 2012). Infectious diseases and parasitic protozoa remain a major threat to the health of the population throughout the world. However, while there are few effective medicines for the treatment of many protozoal diseases, therapies for malaria, leishmaniasis and trypanosomiasis related diseases are severe threat to more than 2 billion people who reside in the developing world.

Interest in plant products has been stimulated by the identification of the antiplasmodial activity of the sesquiterpene lactone artemisinin. This experience is not being ignored; on the contrary, it is being reinforced as plants have frequently provided template molecules on which to base further novel structures. This has been the case, at least, for the past 50 years where antimicrobials and anti-parasitic medicines have been identified from the products of fungi and bacteria and this further consolidates the need to look into these resources for novel leads.

It has been observed that parasitic diseases usually cannot be treated with a single compound. It is also a fact that pure natural products while serving as lead structures have restricted use in humans as they have associated toxicity. On the other hand, many natural compounds with a desired profile of activity have low toxicity but cannot progress into preclinical studies because of their low bioavailability and/or poor solubility. Nonetheless, chemists have been able to create safer compounds which are close to the lead compound and have reduced toxicity; greater bioavailability and with reduced toxicity. There are nonetheless, gaps in our knowledge in terms of safety and general interactions with other medicines. Thus, the potential that natural products present in terms of potential development along with the talents of synthetic chemists can contribute to both anti-parasitic drug research and aim at producing new and urgently needed medicines in the future.

Parasitic diseases, especially those defined as neglected diseases by the WHO, remain a major public health problem, which affects hundreds of millions of people especially in developing countries. Among the important life-threatening diseases is malaria and it is the single most important cause of ill health, mortality and poverty in Sub-Saharan Africa. It kills on average 1.5 million people annually and the majority of them being children (WHO, 2010). The re-emergence of malaria in many parts of the world is due to the rapid increase of resistance to most of the available anti-malarial drugs, as well as resistance of vectors to insecticides. Drug-resistant strains of *P. falciparum* are emerging in many endemic areas of the world highlighting the failure of conventional antimalarial drugs. The difficulty over the past decades at creating an efficient vaccine as well as the observed side effects of existing anti-malarial medicines have implied the urgent necessity to research and develop well-tolerated anti-malarials drugs both for the treatment of the prophylaxis and to help eliminate the parasite (Krishan *et al.*, 2006; Willcox and Bodeker, 2004).

2. Malaria

Despite all efforts made to eradicate malaria, the mortality and morbidity still increase each year mainly because of drug resistance of *Plasmodium falciparum*. WHO estimates that with 300-500 million clinical cases and more than 2 million deaths each year, malaria remains one of the three most deadly communicable diseases in the world (WHO, 2010). History has revealed that plants are still important sources of medicine against malaria (Musuyu Muganza *et al.*, 2012).

The classical antiprotozoal drug that has been used against malaria is quinine, extracted from the *Cinchona* bark. Whilst it is still occasionally being used, it has served a very important purpose, especially in the wake of growing resistance to *P. falciparum* – it has been used as a template for the production of newer semi-synthetics such as chloroquine, mefloquine and others, which are under development.

The discovery of Artemisinin, derived from the Asiatic wormwood, *Artemisia annua* has boosted research on plants with potential for treating malaria. The antiprotozoal potential of sesquiterpenes and sesquiterpene endoperoxide in addition to artemisinin has been extensively sought after ever since the potential of the latter has been demonstrated against malaria. The exocyclic methyl lactone found in Parthenin (identified as the allergic principle in some medicinally used plants especially those derived from the Asteraceae family) is showing promise against *P. falciparum*, *in vitro*. Parthenin derivatives with the exocyclic methyl lactone

have been synthesized and retested. Artemisinin has also given the more stable derivative – Artemether. With the observed and confirmed activity of Artemisinin, the antiplasmodial flavonoids (Figure 1) from *Artemisia annua* have attracted renewed interest. Recently, it has been demonstrated that the methoxylated flavonones artemetin and casticin can act synergistically with artemisinin against *P. falciparum in vitro*. Other studies on the *Artemisia* genus have generated interesting results. For instance, *Artemisia vulgaris* from Thailand have led to the isolation of sakuranetin and 7-methoxyaromadendrin which are very active, *in vitro* (Phillipson and Wright, 1991; Pradines *et al.*, 2011; Muthaura *et al.*, 2011).

The Asteraceae family has also contributed other interesting plants - the *Vernonia* species. It was the observations made on wild chimpanzees chewing the young stems of *Vernonia amygdalina* have led to the isolation of vernodalin and vernolides and hydroxyverniladin (Ohigashi *et al.*, 1994). These molecules are nowadays being tested for their antitumor properties (Khalafalla *et al.*, 2009).

Interestingly, while *Artemisia afra* does not contain the exocyclic methyl lactone, it has been used on the continent against malaria (Gathirwa *et al.*, 2007). Recent investigations on this plant are showing interesting applications in controlling mycobacterial applications (Ntutela *et al.*, 2009). Another African Asteraceae showing promise is *Dicoma tomentosa*. This plant is being used in Burkina Faso against malaria. The active compound, with moderate activity, was urospermal A-15-O-acetate. Studies are ongoing to further assess the safety of this plant by the local population (Jansen *et al.*, 2012).

Other molecules isolated from plant sources comprise Lapacho, which contains quinone and also exhibits antiprotozoal properties. It is also used against cancer treatment. *Diospyros* spp. are also used by local people for similar purposes. Prenylated xanthones isolated from plants from the Clusiaceae family, namely *Garcinia cowa*, have demonstrated significant activity against *P. falciparum in vitro*. Cowaxanthone has displayed an antiplasmodial potential comparable to pyrimethamine. While several biological properties (antibacterial, antifungal and cytotoxic) have been attributed to the xanthones, there are very few reports on the antiplasmodial activity of these compounds (Riscoe *et al.*, 2005; Mahabusarakam *et al.*, 2006).

Finally, one species that has shown promise *in vitro* is Cryptolepin, isolated from *Cryptolepis sanguinolenta* (Periplocaceae) was also found to be active, *in vitro*, against *P. falciparum* (Cimanga *et al.*, 1997). Clinical studies have been performed on this plant extract with a view to comparing its efficacy with that of chloroquine using the WHO extended 7 days *in vivo* test to measure patients with parasitaemia response. A number of malaria patients with parasitaemia of 10.000-100.000 *P. falciparum* per 8000 white blood cells were used. The results indicated that the efficacy of an aqueous extract was comparable to that of chloroquine. Interestingly, no recrudescence of parasitaemia occurred after a follow-up period of 21 days. Other clinical symptoms such as fever, headaches etc. cleared faster in the group treated with the herbal preparation (Boye *et al.*, 2002).

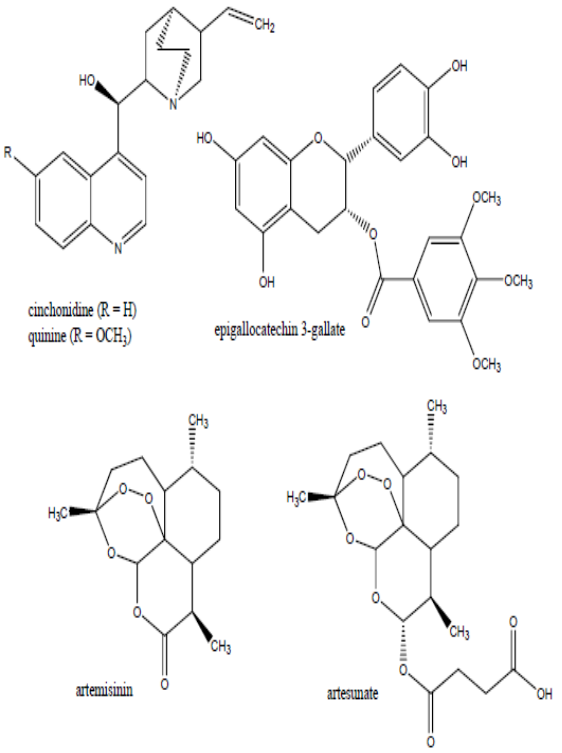

Figure 1. Examples of anti-malarial secondary metabolites. Artesunate is a semisynthetic derivative of artimisinine (Wink, 2012).

3. Leishmania

Leishmaniasis is a severe human disease that is endemic to Africa, America, the Indian subcontinent, subtropical South West Asia as well as many parts of the Mediterranean. In 2009, the disease had accounted for 50, 000 deaths and affected nearly 10 million people worldwide (WHO, 2010). The disease currently threatens about 350 million people in 88 countries around the world, with about 2 million affected annually (Musuyu Muganza *et al.*, 2012). The clinical manifestations vary with the species of the protozoa. They are obligatory intracellular protozoans living in macrophages of mammalian hosts. The extra cellular stage, the promastigote, is introduced into subcutaneous tissues in the human host during the bite of an infected sand-fly vector, *Phlebotomus* (Old World) and *Lutzomyia* (New World). The promastigote is phagocytosed by a mononuclear phagocyte, after which it converts into the obligatory intracellular form, the amastigote. There are two general forms of the disease: visceral leishmaniasis caused by *L. donovani* and *L. infantum* = *L. chagasi* and tegumentary leishmaniasis caused by several dermatropic species of *Leishmania*. This disease is the third largest after malaria and filariasis. Visceral Leishmania causes almost 5000.000 new cases per year globally and almost 90% occurring in just 5 countries (India, Brazil, Bangladesh, Nepal and Sudan). The tegumentary form of the disease, although not as killing as the visceral form,

affects over 1.5 million and causes disfigurement, disability and associated social and psychological stigma.

There is at present, no vaccines against this disease and most of the medicines are mineral based. Unfortunately, such medicines elicit toxic effects, teratogenicity as well as increasing resistance. Antifungal polyene antibiotic is being used in industrialized countries but there have been some relapses in cases of joint infections HIV/*L. infantum*. Often the control of this disease includes the use of pesticides to destroy the vector, improvement of the hygiene and water supplies, as well as targeting the parasite. The latter often takes different forms throughout its lifecycle, making elimination difficult.

The lack of an effective antileishmanial medicine has caused a renewed interest in the study of medicinal plants as source of new chemotherapeutic compounds with better activities and fewer side effects (Khaliq *et al.*, 2009). Natural products in an era of rational drug design still play an important role in the search for new active drugs as they represent valuable lead structures that can de developed further into useful therapeutics. Cragg and Newmann (2007) have shown that many of the drugs approved recently are derived from natural sources. Cordell also reported that 'natural products offer a diversity of structures that simply cannot be matched through even the most active imaginations of the synthetic chemist (Cordell, 2000).

The search from Nature is on and many compounds are still being discovered with good antileishmanial activities. *Garcinia lucida* (Clusiaceae) have yielded chelerythrine derivatives, which manifest significant activities against *L. donovani* (Fotie *et al.*, 2007). Artemisinin from *Artemisia annua* leaves and seeds (Islamuddin *et al*., 2012, Sen *et al.*, 2007), alkenyl phenol (gibbilimbol B), isolated from *Piper malacophyllum*, has been found, for the first time, to trigger induction of cell-cycle arrest and apoptosis and disrupt the leishmania plasma membrane upon initial incubation, *in vitro*. Derivatives are currently being synthesized for the development of therapeutic agents against both leishmaniasis and Chagas diseases (de Oliviera *et al.*, 2011).

Recent screenings of essential oils from *Coriandrum sativum*, *Lippia sidoides* and the oleoresin from *Copaeifera reticulata* on the promastigotes and amastigotes of *Leishmania chagasi* have shown that the resin of *C. reticulata* could be a viable option for analyzing the *in vivo* therapeutic effects of leishmanicidal plants (Rondon *et al*., 2012).

A number of natural products have already been screened. Among natural products from marine sources cyclic peptides, various flavonoids, chalcones, lignans, coumarins, iridoids, monoterpenes, saponins, toxoids, curcumin, quinoline alkaloids, and polyketides exhibit interesting anti-leishmanial activities. Active flavanones and flavonoids were reported from *Baccharis retusa*(Asteraceae) and *Kalanchoe pinnata* (Crassulaceae) (Wink, 2012). Warifteine, a Bisbenzylisoquinoline alkaloid, isolated from *Cissampelos sympodialis* is also an attractive candidate as it induces changes in the parasite morphology and notwithstanding the fact that the plant is commonly being used in Brazilian folk medicine against various diseases (da Silva *et al.*, 2012). Allicin (diallyl thiosulphinate), extracted from garlic, has been tested for its anti-leishmanial activity. The low toxicity of mammalian cells of this compound has opened avenues for a combined therapy against leishmania infections (Jesus Corral-Caridad *et al.*, 2012).

A very promising phytochemical, peganine hydrochloride dihydrate was identified as an orally active antileishmanial lead molecule from the seeds of *Peganum harmala*. *P. harmala* Linn, commonly known as 'harmal' belonging to the family Zygophyllaceae, is one of the most important medicinal plants of India. Its different parts are used in traditional systems of medicine for the treatment of variety of human ailments. The potent compound showed a simple structure, easily synthesizable, non-toxic to hosts and induces apoptosis-like cell death in *L. donovani*. The binding interactions between compound 1 from *L. donovani* and DNA topoisomerase I in molecular modeling studies (docking) and experimental studies suggested that the apoptosis like cell death appears to be due to *L. donovani's* topoisomerase I inhibition by 1. Further work is under consideration to study the pharmacokinetic, pharmacodynamic and toxicological studies of compound 1 and also to synthesise the analogues of 1 to develop more potent anti-leishmanial agent than natural lead (Misra *et al*., 2008).

4. Human African Trypanosomiasis

Human African trypanosomiasis (HAT) is a fatal, if untreated, fly-borne neuroinflammatory disease caused by protozoa of the species *Trypanosoma brucei* (*T.b.*). The increasing trend of HAT cases has been reversed, but according to WHO experts new epidemics of this disease could appear (Seke and Mahomoodally, 2012).

In sub-Saharan Africa, several Trypanosoma species cause important veterinary diseases, but only two cause significant suffering in man: *Trypanosoma b. gambiense* and *Trypanosoma b. rhodesiense*, respectively, causing chronic and acute sleeping sickness. Indeed, HAT is still a considerable burden for quality of life and economy in 36 sub-Saharan Africa countries with 15-20 million persons at risk. HAT may results in a 100% mortality rate if left untreated (Musuyu Muganza *et al.*, 2012). Following joint initiatives of WHO and private partners, the fight against HAT was re-engaged, resulting in considerable breakthrough. Although HAT has had a heavy toll on the health and economy of about 36 African countries, effective and satisfactory chemotherapy has not been found against the causative agents; *Trypanosoma brucei gambiense* which is responsible for chronic form of HAT in West and Central Africa, and *Trypanosoma brucei rhodesiense*, the etiological factor for the acute form of the disease in East Africa.

To this effect, the last few decades have witnessed a plethora of investigations which have been geared to investigate the effect of common traditionally-used medicinal plants in alleviating the cellular changes *in vivo* produced during the *T. b. brucei* infections of rats. A number of medicinal plants and secondary metabolites

isolated from them have been screened for anti-trypanosomal activity. Traditional knowledge was the basis for the selection of plants and one study included *Landolphia uniflora, Momordica balsamina* pulp, *Aloe vera* pulp, *Annona senegalensis, Securidaca longipenduculata* root and root bark. Based on folk medicines they were claimed to possess antiprotozoal activity and alleviate one or many of the clinical symptoms such as intermittent fever, immunosuppression, anemia, jaundice and hepatomegaly commonly associated with trypanosomiasis. Interestingly, it was found that these plants had the potential in the management of HAT due to *T. b. brucei*. *Momordica balsamina* and *S. longipenduculata* were found to possess the highest potential since they are able to control anemia by resisting sudden drop in packed cell volume values (Abubakar *et al.*, 2005).

Recently, Musuyu Muganza *et al.* (2012) reported *in vitro* antiprotozoal and cytotoxic activity of 33 ethonopharmacologically selected medicinal plants from Democratic Republic of Congo. It was found that most of the tested extracts exhibited pronounced ($IC_{50} \leq 5$ µg /ml) or good ($5 < IC_{50} \leq 10$ µg/ml) antiprotozoal activity against one or more of the selected protozoa. A total of 19 plant extracts inhibited *Trypanosoma b. brucei*, especially the extract from Isolona hexaloba stem bark (IC_{50} = 1.95 µg /ml, SI = 16.5); 8 plant extracts were active against *Trypanosoma cruzi*, the extracts from *Enanatia chlorantha* stem bark and *Quassia africana* root bark being the most active with IC_{50} values of 1.87 and 1.88 µg/ml, respectively (SI = 3.0 and 3.3, respectively); 8 plant extracts showed activity against *Leishmania infantum*, with extracts from *Napoleona vogelii* stem bark and *Quassia africana* root bark as the most active with IC_{50} values of 5.66 and 5.04 µg/ml (SI = 11.3 and 1.2). Finally, the authors reported 9 plant extracts inhibited *Plasmodium falciparum* K1 with the extracts from *Quassia africana* (root bark and stem bark) being the most active ones with IC_{50} values of 0.46 and 1.27 µg/ml (SI = 13.7 and 13.6). Extracts from *Enantia chlorantha* stem bark, *Piptadeniastrum africanum* stem bark and *Quassia africana* root bark were cytotoxic for MRC-5 cells ($CC_{50} < 10$ µg /ml).

In another study, extracts of *Hymenocardia acida* stem bark exhibited significant trypanocidal activity whereas *Gardenia erubescens* and *Lophira lanceolata* were effective at Minimum Inhibitory Concentration (MIC) of 20 mg/ml (Abu *et al.*, 2009). Nigerian plants were also evaluated *in vitro* for trypanocidal activity against *T.b. brucei* and *T. congolense* at concentrations of 4 mg/ml, 0.4 mg/ml and 0.04 mg/ml. It was found that extracts of *Khaya senegalensis, Piliostigma reticulatum, Securidaca longepedunculata* and *Terminalia avicennoides* were strongly trypanocidal to both organisms while extracts of *Anchomanes difformis, Cassytha spp, Lannea kerstingii, Parkia clappertioniana, Striga spp, Adansonia digitata* and *Prosopis africana* were trypanocidal to either *T. b. brucei* or *T. congolense*. *Kigelia africana*, from Kenya was also evaluated *in vivo* and was found that the dichloromethane fruits extract of *K. africana* tested at a dose of 2000 mg/kg was effective, curing 60% of the Swiss white mice that had previously been inoculated with *T. b. rhodesiense* KETRI 3798 (Atawodi *et al.*, 2003; Peter *et al.*, 2009).

In another investigation, *Scoparia dulcis* was evaluated on the population of immune cells during a 28 day experimental *T. brucei* infection in rabbits. The result obtained showed that infection resulted in an initial rise in both total WBC and the absolute number of circulating lymphocytes followed by a progressive decrease in total WBC and all WBC subtypes (lymphocytes, monocytes and granulocytes), although the percentage of lymphocytes remained consistently higher than normal throughout the study period. These changes were consistent with the development of trypanosome-induced immunosuppression in their mammalian host and interestingly, treatment with *S. dulcis* at a daily oral dose of 25 mg/Kg body weight was found to significantly reduce the severity of the observed lesions when compared with untreated infected animals. Thus *S. dulcis* was classified as a potential herb that had demonstrated significant potency in protecting against the parasite induced decrease in the population of immunologically active cells (Orhue *et al.*, 2009).

From the above key investigations, it is clear that these findings provide strong evidence of the potential beneficial effects of phytotherapy in the traditional management of trypanosomiasis, which could be subsequently developed into a cost effective alternative medicine to complement treatment of trypanosomiasis.

Nonetheless, several investigations tend to suggest that it is often difficult to probe the exact mode of action by which these plants extracts exhibit their trypanocidal action. Indeed, the possible mechanisms by which these plants extracts and phytochemicals therein carry out this role remain a subject of great speculations and debate in the scientific community. Several possible mechanisms working separately or in concert may account for the observed effect (Orhue *et al.*, 2009).

In one study, it was suggested that different phyto-compounds could be responsible and operate in a synergistic effect for the observed anti-trypanocidal activities. Interestingly, preliminary phytochemical screening of potent plants against trypanosome showed the presence of known bio-active compounds such as saponins, tannins, flavonoids and alkaloids in the crude plant extracts tested. Several authors have also identified or isolated tannins and phenolic compounds, flavonoids and alkaloids in plants that showed significant trypanocidal activities (Freiburghaus *et al.*, 1996). Active natural products include several groups of alkaloids, phenolics, saponins, cardiac glycosides, other terpenoids, and polyacetylenes (common in Apiaceae, Asteraceae and Araliaceae). Although some natural products are active in the sub-micromolar range and show good selectivity, only few have been studied *in vivo* in an animal model. None of these results have been translated into clinical practice (Wink, 2012).

Accumulated evidence also suggest that many natural products exhibit their trypanocidal activity by virtue of their interference with the redox balance of the parasites acting either on the respiratory chain or on the cellular defenses against oxidative stress. For instance, the observed trypanocidal activity of *K. africana* extract was

justified due to the increase of oxygen consumption and stimulation of hydrogen peroxide production in the protozoan cell. Trypanosoma do not have the same biochemical mechanism as mammalian cells for dealing with excess peroxide and consequent oxygen free radicals (Peter *et al.*, 2009). Furthermore, it is proposed that natural products possess structures capable of generating radicals that may cause peroxidative damage to trypanothione reductase that is very sensitive to alterations in redox balance. It is also known that some agents act by binding with the kinetoplast DNA of the parasite.

On the other hand, investigations undertaken by Freiburghaus *et al.* (1996) and Atawodi *et al.* (2003) have clearly indicated that different solvent extracts of the same plant may exhibit different trypanocidal activity just as extracts of different parts of the same plants. Therefore, the statement that a plant is trypanocidal or not should be taken within the context of the solvent used and the parts investigated. On the other hand, out of the 40 plant extracts tested by Nibret and Wink *et al.* (2010) and Nibret *et al.* (2010), the dichloromethane extract from stem bark of *Warburgia salutaris* (claimed to be used against many pathologies in many parts of Africa) was found to exhibit the most potent trypanocidal activity. The trypanocidal activity was suggested to be due to the drimane sesquiterpenoids (warburganal, polygodial). Concerning the mechanism, it was proposed that the two sesquiterpene aldehydes, warburganal and polygodial, formed covalent bonds with amino groups of proteins and affect a vast number of cellular activities. In another groundbreaking *in vitro* study, the authors were able to isolate the pregnane glycosides from genus *Caralluma* (*C. Penicillata, C. tuberculata* and *C. russelliana*) and evaluated for the trypanocidal activity. It was found that the penicilloside E possess the highest anti-trypanosoma activity followed by caratuberside C, which exhibited the highest selectivity index (Abdel-Sattar *et al.*, 2009).

Studies have shown that it is probable that the etiology of trypanosome-induced leucopenia in rabbit may be similar to the case with trypanosome-induced anemia. There has been striking indications that the onset of anemia in HAT may be strongly related to disruption of erythrocyte membrane caused directly by parasite attack on red cells. It has also been suggested that products secreted by the parasite may play a significant role in the disruption of red cell membrane.

Reduction in red cell membrane sialoglycoprotein secondary to elevated activity of plasma sialidases promotes the rapid destruction of erythrocytes. A role for parasite and macrophage-derived free radicals and proteases in the pathogenesis of trypanosome-induced anemia has also been postulated (Orhue *et al.*, 2009). The possibility that *S. dulcis* or certain components of the herb may help stabilize the membrane of blood cells cannot be out rightly dismissed. Specifically, the anti-oxidant or free radical scavenging properties of *S. dulcis*, may play vital roles in this regard especially against the backdrop of the role of free radicals in the pathogenesis of *T. brucei* infection. Furthermore, increased production of blood cells may help in replenishing of these cells. In the absence of any evidence of possible trypanocidal activity for the herb, it does not seem an attractive option to speculate that the higher level of immunological cells in treated animals could be due to the destruction of the parasite by agents native to the plant (Orhue *et al.*, 2009).

Trypanosomes lack catalase and glutathione peroxidases but have evolved a unique system with trypanothione to detoxify hydroperoxide. Trypanothione is built from two molecules of glutathione and one molecule of spermidine (Figure 2). Inactivation of the enzymes of trypanothione, spermidine or glutathione biosynthesis or of trypanothione directly will lead to death of the parasite. The synthetic drug eflornithine (see above) inhibits ornithine decarboxylase which is important for spermidine biosynthesis. It is likely that secondary metabolites which can bind to the SH-group of trypanothione exhibit anti-trypanosomal activity. This has been shown for polyacetylenes which carry a reactive triple bond that can easily alkylate SH groups; e.g., the polyacetylene Carlina oxide from *Carlina acaulis* (Asteraceae) (Figure 2) and polyacetylenes from ginseng (*Panax ginseng*) have significant cytotoxic activity against *T. b. brucei* but are hardly toxic to human cells.

On the other hand, (Adeyemi *et al.*, 2009) have showed that *Psidium guajava* leaf extract has trypanocidal properties and has attributed these effects in parts to the broad antimicrobial and iron chelating activity of flavonoids and tannins respectively. They have also proposed that iron chelation is an effective way of killing trypanosomes and the prime target is the enzyme, ribonucleotide reductase whose activity is central to DNA synthesis prior to cell division as depicted in trypanosomiasis infection.

Another target is DNA topoisomerase I; camptothecin, a known inhibitor of DNA Topo I also inhibits *T. brucei* with an IC_{50} of 1.5 μM. The aporphine alkaloid dicentrine which is present in Papaveraceae and Lauraceae inhibits DNA Topo II and is active against trypanosomes. Inhibitors of farnesyl transferase and tubulin polymerisation (e.g., vinblastine, sanguinarine) have substantial anti-trypanosomal activities (Wink, 2012).

Moreover, a plant with high *in vitro* trypanocidal activity may have no *in vivo* activity and vice versa, because of peculiarities in the metabolic disposition of the plant's chemical constituents. Therefore, plants found to be active in the above-mentioned investigations must be tested *in vivo* and tested clinically before a definite statement can be made on their trypanocidal potentials (Atawodi *et al.*, 2003).

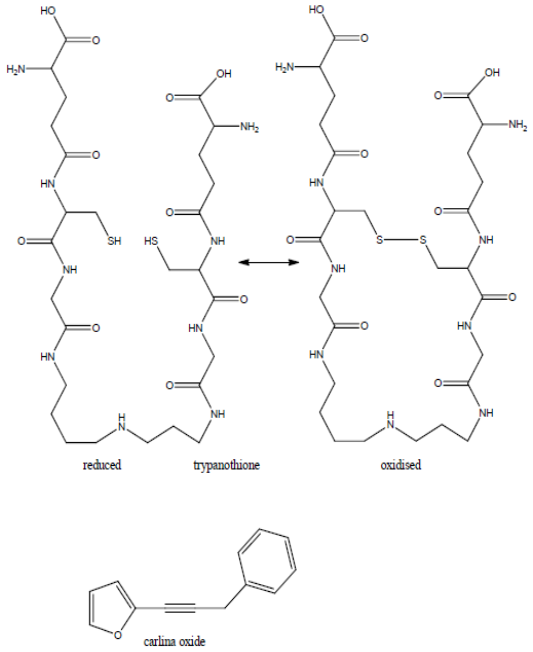

Figure 2. Reduced and oxidised form of trypanothione and carlina oxide which can block the SH-groups of trypanothione (Wink, 2012).

5. Conclusion And Future Perspectives

Evidently, many investigators indicate that traditional medicines might offer potential template molecules in the drug discovery process. Indeed, the discovery of compounds with anti-parasitic and antimicrobial activities from traditional medicinal plant remedies remains a medically and potentially challenging task. For malaria and trypanosomiasis quite a number of medicinal plants and isolated natural products such as alkaloids, phenolics, saponins, cardiac glycosides, and terpenoids, amongst others have already been tested, but for most of the other parasitic diseases such information is largely missing.

On the other hand, to adventure in such an endeavor, highly reproducible and robust innovative bioassays are needed in view of our limited understanding of the multi-factorial pathogenicity of such infectious diseases. To this effect, it is of utmost importance for investigators to embark and devise new automated bioassays with special emphasis on high through-put procedures that can screen and process data from a panoply of phytochemicals within shorter time lapse. Additionally, these procedures should also attempt to rule out false positive hits and de-replication methods to remove nuisance compounds. The ultimate goal will be to establish structure-activity phytochemical libraries to boost new antimicrobials drug discovery.

Nonetheless, despite continuous comprehensive and mechanism-orientated evaluation of medicinal plants worldwide, there is still a dearth of literature coming from the last decade's investigations addressing procedures to be adopted for quality assurance, authentication and standardization of crude plant products. Finally, above and beyond simple *in vitro* and *in vivo* assays, randomized controlled trials using standardized products or products containing pure plant extracts must be carried out and reported for each claim.

References

Abubakar A, Iliyasu B, Yusuf AB, Igweh AC, Onyekwelu NA, Shamaki BU, Afolayan DO and Ogbadoyi EO. 2005. Antitrypanosomal and haematological effects of selected Nigerian medicinal plants in Wistar rats. *Biokemistri*., **17**: 95-99.

Abu AH, Uchendu CN and Ofukwu R.A. 2009. *In vitro* anti-trypanosomal activity of crude extracts of some Nigerian medicinal plants. *J. Appl. Biosc*., **21**: 1277-1282.

Abdel-Sattar E, Shehab NG, Ichino C, Kiyohara H, Ishiyama A, Otoguro K, Omura S and Yamada H. 2009. Antitrypanosomal activity of some pregnane glycosides isolated from Caralluma species. *Phytomedicine*., **16**: 659-664.

Adeyemi OS, Akanji MA and Oguntoye SA. 2009. Ethanolic leaf extract of *Psidium guajava*: Phytochemical and trypanocidal activity in rats infected with *Trypanosoma brucee brucei. J. Med. Plants Res.*, **3**: 420-423.

Anon. 2008. World Health Organisation. www.who.int/mediacentre/factsheet/fs134/en

Atawodi SE, Bulus T, Ibrahim S, Ameh DA, Nok AJ, Mamman M and Galadima M. 2003. *In vitro* trypanocidal effect of methanolic extract of some Nigerian savannah plants. *Afri. J. Biotechnol.*, **2**: 317-321.

Bashar S, Hassan A and Omar S. 2005. Tradition and Perspective of Arab Herbal Medicine: A Review. *eCAM*, 1-5.

Bashar S, Hassan A and Omar S. 2008. Arab Herbal Medicine. In: Ronald R. Watson and Victor R Preedy (Eds), Botanical Medicine in Clinical Practice, CABI, UK.

Boye GL, Bugyei K, Addy ME, and Ofori-Adjei D. 2002. Clinical efficacy of Phyto-Laria, a teabag formulation of *C. sanguinolenta* root, The Food and Drugs Board, Medical School, University of Ghana.

Cimanga K, De Bruyne T, Pieters L, and Vlietinck AJ.1997. *In vitro* and *in vivo* antiplasmodial activity of cryptolepin and related alkaloids from *Cryptolepis sanguinolenta. J. Nat. Prod.*, **60**: 688-669.

Coker R, Atun R, and McKee M. 2008. Health Systems and the Challenge of Communicable Diseases Experiences from Europe and Latin America. McGraw-Hill Education, Open University Press. England.

Cordell G. 2000. Biodiversity and drug discovery - a symbiotic relationship. *Phytochemistry*., **55**: 463-480.

Cragg G and Newmann GM. 2007. Natural products as sources of new drugs over the last 25 years. *J. Nat. Prod*., **70**: 461-477.

da Silva E, Dias Rayol C, Lys Medeiros P, Figueiredo R, Piuvezan M, Brabaso-Filho J, Fernandes Marinho A, Silva T, Militao G, Pimentel Cassilhas A, and Paes de Andrade P. 2012. Study of the activity of 3-benzyl-5-(4-chloro-arylazo)-4-thioxo-imidazolidin-2-one against *Schistosomiasis mansoni* in Mice. *Scientific World J.*, **2012: 520524.**

de Oliviera A, Mesquita JT, Tempone AG, Lago JH, Guimaraes EF and Kato MJ. 2012. Leishmanicidal activity of an alkenylphenol from piper malacophyllum is related to plasma disruption. *Exp. Parasitol*., **132**: 383-387.

Fotie J, Bohle DS, Olivier M, Gomez MA, and Nzimiro S. 2007. Trypanocidal and antileishmanial dihydrochelerythine derivatives from *Garcinia lucida*. *J. Nat. Prod.*, **70**: 1650-1653.

Freiburghaus F, Kaminsky R, Nkunya MH, and Brun R. 1996. Evaluation of African medicinal plants for their *in vitro* trypanocidal activity. *J. Ethnopharmacol*., **55**: 1-11.

Gathirwa JW, Rukunga GM, Njagi ENM, Omar SA, Guantai AN, Mathaura CN, Mwitari PG, and Ndiege IO. 2007. *In vitro* antiplasmodial and *in vivo* antimalarial activity of some plants

traditionally used for the treatment of malaria by the Meru community in Kenya. *J. Nat. Med*., **61**: 261-268.

Heinrich M, Barnes J, Gibbons S and Williamson EM. 2004. Fundamentals of Pharmacognosy and Phytotherapy. Churchill Livingstone, Elsevier Science Ltd., UK

Islamuddin M, Farooque A, Dwarakanath B, Sahal D and Afrin F. 2012. Artemisia annua leaves and seeds mediate programmed cell death in *Leishmania donovani*. *J. Med. Microbiol*., **61**: 1709-1718.

Jansen O, Tits M, Angenot L. Nicolas J, De Mol P, ikiema J and Frédérich M. 2012. Anti-plasmodial activity of *Dicoma tomentosa* (Asteraceae) and identification of urospermal A-15-O-acetate as the main active compound. *Malaria J.* **11**: 289 doi:10.1186/1475-2875-11-289.

Jesus Corral-Caridad M, Moreno I, Torano A, Dominquez M and Alunda JM .2012. Effect of allicin on promastigotes and intracellular amastigotes of *Leishmania donovani* and *L. infantum*. *Exp. Parasitol*., **132**: 475-482.

Khaliq T, Misra P, Gupta S , Reddy KP, Kant R, Maulik PR, Dube A and Narender T. 2009. Peganine hydrochloride dihydrate an orally active antileishmanial agent. *Bioorg. Med. Chem. Lett.*, **19**: 2585-2586.

Khalafalla M, Abdellatef E, Daffalla HM, Amr A. Nassrallah AA, Aboul-Enein KM, David A. Lightfoot DA, Cocchetto A and El-Shemy HA. 2009. Antileukaemic activity from root cultures of *Vernonia amydalina*. *J. Med. Plants Res*., **3**: 556-562.

Krishna S, Woodrow CJ, Staines HM, Haynes RK and Mercereau-Puijalon O. 2006. Re-evaluation of how artemisinins work in light of emerging evidence of *in vitro* resistance. *Trends Mol. Med*., **12**: 200-205.

Mahabusarakam W, Kuaha K, Wilairat P and Taylor WC. 2006. Prenylated xanthones as potential antiplasmodial substances. *Planta Med.*, **72**: 912-916.

Misra P, Khaliq T, Dixit A, SenGupta S, Samant M, Kumari S, Kumar S, Kushawaha P, Majumder H, Saxena A, Narender T, and Dube A. 2008. Antileishmanial activity mediated by apoptosis and structure-based target study of peganine hydrochloride dihydrate: an approach for rational drug design. *J. Antimicrob. Chemther*., **62**: 998-1002.

Musuyu Muganzaa D, Fruthb BI, Nzunzu Lamia J, Mesiaa GK, and Kambua, OK. 2012. *In vitro* antiprotozoal and cytotoxic activity of 33 ethnopharmacologically selected medicinal plants from Democratic Republic of Congo. *J. Ethnopharmacol*., **7**: 301-308.

Muthaura CN, Keriko JM, Derese S, Yenesew A, Rukunga GM. 2011. Investigation of some medicinal plants traditionally used for treatment of malaria in Kenya as potential sources of antimalarial drugs. *Exp. Parasitol*., **3:** 609-626.

Nibret E. and Wink M. 2010. Volatile components of four Ethiopian *Artemisia* species extracts and their *in vitro* antitrypanosomal and cytotoxic activities. *Phytomedicine*., **17**: 369-374.

Nibret E, Ashour ML, Rubanza CD, and Wink M. 2010. Screening of some Tanzanian medicinal plants for their trypanocidal and cytotoxic activities. *Phytother. Res*., **24**: 945-947.

Ntutela S, Smith P, Matika L, Mukinda J, Arendse H, Allie N, Estes DM, Mabusela W, Folb P, Steyn L, Johnson Q, Folk WR, Syce J and Jacobs M. 2009. Efficacy of Artemisia afra Phytotherapy in experimental tuberculosis. *Tuberculosis*., **89**: S33-S40.

Nunkoo D and Mahomoodally F. 2012. Ethnopharmacological survey of native remedies commonly used against infectious diseases in the tropical island of Mauritius. *J. Ethnopharmacol*., **28**: 548-564.

Nhigashi H, Huffman M and Izutsu D.1994. Towards the chemical ecology of medicinel plant use in chimpanzees: the case of Vernonia amygdalina, a plant used by wild chimpanzees possibly for parasite-related diseases. *J. Chem. Ecol*., **20**: 541-553.

Orhue N, Nwanze E and Okafor A. 2009. *Scoparia dulcis* protects against *Trypanosoma brucei* induced immunosuppression in experimentally infected rabbits. *Afri. J. Food Sci*., **3**: 172-175.

Peter O, Magiri, E., Auma J, Magoma G, Imbuga M and Murilla G. 2009Evaluation of in vivo antitrypanosomal activity of selected medicinal plant extracts. *J. Med. Plants Res*., **3**: 849-854.

Phillipson D and Wright C. 1991. Can ethnopharmacology contribute to the development of antimalarial agents? *J. Ethnopharmacol.*, **32**: 155-165.

Riscoe M, Kelly JX and Winter R. 2005. Xanthones as antimalarial agents: discovery, mode of action, and optimization. *Curr. Med. Chem.*, **12**: 2539-2549.

Rondon FC, Bevilaqua CM, Accioly MP, Andrade-Junior HF, Lima JC and Magalhaes HC. 2012. *In vitro* efficacy of *Coriandrum sativum, Lippia sidoides* and *Copaifera reticulata* against *Leishmania chagasi. Rev. Bras. Parasitol. Vet.*, **21**: 185-191.

Seke P and Mahomoodally F. 2012. New insights in staging and chemotherapy of African trypanosomiasis and possible contribution of medicinal plants. *Scientific World J*., **2012**: 436039.

Sen R, Bandyopadhyay S, Dutta A, Mandal G, Ganguly S, Saha P and Chatterjee M. 2007. Artemisinin triggers induction of cell-cycle arrest and apoptosis in Leishmania promastigotes. *J. Med. Microbiol.*, **56:** 1213-1218.

WHO 2005. Leishmaniasis background information. http://www.who.int/leishmanisis/en/

WHO 2010. World Malaria Report 2010, Available at http://who.int/malaria/worldmalariareport2010/worldmlariareport .pdf.

Willcox ML and Bodeker G. 2004. Traditional herbal medicines for malaria. *BMJ*., **329**:1156-1159.

Wink M. 2012. Medicinal Plants: A source of anti-parasitic secondary metabolites. *Molecule.*, **17**:12771-12791.