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Chemopreventive and remediation effect of *Adansonia digitata L.* Baobab (Bombacaceae) stem bark extracts in mouse model malaria

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ABSTRACT

Ethnopharmacological relevance: *Adansonia digitata L.* Baobab (Bombacaceae) solvent extracts have been reported to possess medicinal properties and are currently been used traditionally for the treatment of malaria and several other diseases and infection; however few reports exist in literature that provides supportive scientific evidence in favour of its medicinal use.

Aim of the study: This study investigated the efficacy of *Adansonia digitata* stem bark extract in offering protection against experimental malaria and also examined its remediation effect when administered after established infection.

Materials and methods: Weanling albino mice were used in the study. The mice were transfected intraperitonially with an inoculums size of 1×10^7 of chloroquine susceptible strain of *plasmodium berghei* infected erythrocytes. Mechanisms of action of the extract were investigated by measuring the degree of tissue peroxidation and tissue antioxidant status. Severity of malaria was determined by measuring the serum C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and serum and tissue Alkaline phosphatase (ALP) activity.

Results: There was a significant increase in serum CRP, TNF-α concentrations and serum and tissue ALP activity in the control mice following *Plasmodium berghei* infection. All the treatment had effect on the growth of *Plasmodium berghei* parasites in mice. The extracts showed a significant dose dependent increase packed cell volume (PCV), percentage chemosupression/clearance and a significant decrease in percentage parasitemia at the two doses when administered after established infection. Methanolic extract (MEAD) at 400 mg/kg exhibited the highest chemosupressive activity. The extract significantly reduced the degree of tissue peroxidation, increased the level of reduced glutathione (GSH), catalase and superoxide dismutase activity. Administration of the extract after established infection reduced serum CRP and TNF-α concentrations and serum and tissue ALP activity.

Conclusion: Our study suggests that *Adansonia digitata* protects against *Plasmodium berghei* induced-malaria, and that administration of the extract after established infection reduced malaria progression.

1. Introduction

Malaria is a mosquito-borne infectious disease of humans and other animals caused by a one-celled obligate intra-erythrocytic protozoan of the genus *Plasmodium*. The disease is transmitted by infective bites from a female Anopheline mosquito or, rarely, through transfusion of infected blood products or in utero from the mother to the newborn through the placenta or during delivery (Malhotra et al., 2006).

The prevalence of malaria remains an ever existing danger for humanity in every part of the globe. In most areas, malaria and poverty co-exist. Malaria is responsible for about 1.3% reductions in economic growth in areas where it is endemic (Sachs and Malaney, 2002). It is frequently referred to as disease of the poor, because it is concentrated in world's poorest countries. Sub-Saharan Africa is the region which is hardest hit by malaria with most countries in the region being highly endemic for malaria transmission (UNICEF, 2007).

According to the world malaria report (WHO, 2015), malaria transmission occurs in five of the six WHO regions, with Europe remaining free. Globally, an estimated 3.2 billion people continue to be at risk of being infected with malaria and developing disease, and 1.2 billion are at high risk (> 1 in 1000 chance of getting malaria in a year).

Plasmodium berghei is a causative agent of rodent malaria and

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usually presents similar cerebral infection equivalent to that by *P. falciparum* in human. The major features of *P. berghei* infection are anaemia, splenomegaly, fever and liver damage (Sudhir and Saxena, 1980). *P. berghei* has a very similar life-cycle to the species that infect humans, and it causes disease in mice which has signs similar to those seen in human malaria. Importantly, *P. berghei* can be genetically manipulated more easily than the species which infect humans, making it a useful model for research into *Plasmodium* genetics (Franke-Fayard et al., 2010).

In the process of studying human malaria parasites, rodent parasites are recognized as valuable model parasites for the investigation of the developmental biology of malaria parasites, parasite-host interactions, vaccine development and drug testing (Menard et al., 1997).

Malaria parasites have stage-dependent high proliferation rates resulting in an increased demand for reducing equivalents. In addition, the high metabolic fluxes of proliferating parasites, the digestion of hemoglobin, and their lifestyle in prooxidant environments lead to an increased endogenous formation of reactive oxygen and nitrogen species. Antioxidant defense, redox regulation, and signaling are thus expected to play crucial roles in *Plasmodium*, represent major targets for chemotherapeutic interventions, and have been shown to be involved in drug resistance (Jortzik and Becker, 2012).

It has been suggested that during their development, malaria parasites are exposed to environmental and metabolic stresses. One strategy to drug discovery was to increase these stresses by interfering with the parasites' antioxidant and redox systems, which may be a valuable approach to disease intervention (Müller, 2015).

In terms of pathogenesis, the host liver is among the organs affected in the early stage of malaria leading to significant alterations in host hepatocyte physiology and morphology. The pathogenesis of hepatic dysfunction is not completely known; reduction in portal venous flow as a consequence of microocclusion of portal venous branches by parasitized erythrocytes, intrahepatic cholestasis due to reticuloendothelial blockage and hepatic microvilli dysfunction, suppression of bilirubin excretion due to effect of parasitemia or endotoxemia or metabolic acidosis, apoptosis and oxidative stress are all mechanisms involved in hepatic damage (Anand and Puri, 2005; Bhalla et al., 2006).

The roles of medicinal plants in preventing and modulating various disease conditions have become important. Medicinal plants are safer and are alternatives to commercial drugs. They are readily available at an affordable cost and are widely distributed by the local population. *Adansonia digitata L.* Baobab (Bombacaceae) is the most widespread of the *Adansonia* species on the African continent, found in the hot, dry savannahs of sub-Saharan Africa. It is recognized as an effective treatment for many diseases. Many parts of the plant have been used traditionally for medicinal and nutritional purposes. The numerous health benefits of *Adansonia digitata* are related to the presence of bioactive compounds (terpenes, saponins, tannins etc.) isolated from its various parts like leaves and fruits (Ramadan et al., 1993). The leaves, bark and fruit pulp have been traditionally used as immunostimulants, analgesics etc. in the treatment of diseases like fever, diarrhoea, cough, dysentery, haemoptysis, tuberculosis and microbial infections (Vermaak et al., 2011). Few reports exist in the literature on the remediation effects of *A. digitata* stem bark extracts in mouse model malaria. However, this study aims at investigating the efficacy of *A. digitata* stem bark extract in offering protection against experimental malaria.

2. Material and methods

2.1. Plant materials: collection and identification

The stem of *Adansonia digitata* (Bombacaceae) was collected from Ido-Ekiti, Ekiti State Nigeria. The plant was identified and authenticated by in the herbarium unit of Forest Research Institute of Nigeria (FRIN) with identification number FHI 109806.

2.2. Preparation of plant extracts

The stem bark peels were air-dried at room temperature to avoid possible degradation or denaturation of their putative compounds. The air-dried stem bark of *Adansonia digitata* was blended to powder using an electric blender. This was stored in a glass container. Blended air-dried stem bark was soaked in sufficient volume of methanol for 72 h at room temperature. It was continually stirred after each 24 h. After 72 h, the mixture was then filtered and the filtrate was concentrated using rotary evaporator at 40 °C. The concentrate was heated over a water bath to obtain a solvent free extract, which was stored in a refrigerator at 4 °C.

2.3. Experimental design

Adult albino mice weighing 20 ± 2 g were divided into six groups (I–VI) of eight animals each.

Group I: Animals were orally administered 200 mg/kg b.w aqueous extract of *A. digitata* stem bark (AEAD).

Group II: Animals were orally administered 400 mg/kg b.w aqueous extract of *A. digitata* stem bark (AEAD).

Group III: Animals were orally administered 200 mg/kg b.w methanolic extract of *A. digitata* stem bark (MEAD).

Group IV: Animals were orally administered 400 mg/kg b.w methanolic extract of *A. digitata* stem bark (MEAD).

Group V: Animals were orally administered the vehicle (5% v/v tween 80) only and served as the control.

Group VI: Animals were orally administered 5 mg/kg b.w chloroquine.

Five animals from each group were sacrificed 5 days after treatment to prepare the serum and tissues homogenates (liver, kidney and heart) which were used for various biochemical analysis. The remaining animals were monitored for post infection.

2.4. Animal handling

The albino mice weighing between 18 and 22 g was obtained from the animal house, Institute of Advance Medical Research and Training (IAMRAT) College of Medicine, University of Ibadan, Nigeria. The animals were acclimatized and housed in individual cage in a temperature and humidity controlled room, having a 12 h light and dark cycle. All the animals had free access to their respective feed and clean drinking water throughout the period of the experiment. All animal experiments were conducted according to the guidelines of National Institute of Health (NIH publication 85-23, 1985) for laboratory animal care and use. The work was approved by the University of Ilorin Ethical Review Committee with approval number UERC/ASN/2015/069.

2.5. Parasites

The *Plasmodium berghei* was obtained from the Institute of Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Nigeria. A standard inoculum of 1×10^7 of parasitized erythrocytes from a donor mouse in volumes of 0.2 ml was used to infect the experimental animals intra-peritoneally.

2.6. Collection and preparation of blood samples

Animals were anaesthetized by putting them in jar containing cotton wool soaked in chloroform. They were allowed to go into unconscious state after which they were brought out for sacrifice. The animals were sacrificed by cutting their jugular veins to collect blood. Part of the blood was collected into EDTA coated bottles to prevent clotting, and preserved for heamatological analysis. The other part of the blood was collected in plain bottles and allowed to clot for the