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The malaria co-infection challenge: An investigation into the antimicrobial activity of selected Guinean medicinal plants

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ABSTRACT

Ethnopharmacological relevance: In sub-Saharan Africa, concomitant occurrence of malaria and invasive infections with micro-organisms such as Gram-positive *Staphylococcus aureus*, Gram-negative *Escherichia coli* and yeasts or fungi such as *Candida albicans* and *Aspergillus fumigatus* is common. Non-tuberculous mycobacteriosis caused by *Mycobacterium chelonae* has been recognized as a pulmonary pathogen with increasing frequency without effective therapy. Although less important, the high incidence of *Trichophyton rubrum* infections along with its ability to evade host defense mechanisms, accounts for the high prevalence of infections with this dermatophyte. Considering the treatment cost of both malaria and microbial infections, along with the level of poverty, most affected African countries are unable to cope with the burden of these diseases. In sub-Saharan Africa, many plant species are widely used in the treatment of these diseases which are traditionally diagnosed through the common symptom of fever. Therefore it is of interest to evaluate the antimicrobial activities of medicinal plants reported for their use against malaria/fever.

Materials and methods: Based on an ethnobotanical survey, 34 Guinean plant species widely used in the traditional treatment of fever and/or malaria have been collected and evaluated for their antimicrobial activities. Plants extracts were tested against *Candida albicans*, *Trichophyton rubrum*, *Aspergillus fumigatus*, *Mycobacterium chelonae*, *Staphylococcus aureus* and *Escherichia coli*.

Results: The most interesting activities against *Candida albicans* were obtained for the polar extracts of *Pseudospondias microcarpa* and *Ximenia americana* with IC_{50} values of 6.99 and 8.12 μg/ml, respectively. The most pronounced activity against *Trichophyton rubrum* was obtained for the ethanol extract of *Terminalia macroptera* (IC_{50} 5.59 μg/ml). Only 7 of the 51 tested extracts were active against *Staphylococcus aureus*. From these, the methanolic extracts of the leaves and stem bark of *Alchornea cordifolia* were the most active with IC_{50} values of 2.81 and 7.47 μg/ml, respectively. Only *Terminalia albida* and *Lawsonia inermis* showed activity against *Mycobacterium chelonae*. None of the tested extracts was active against *Escherichia coli*.

Conclusion: A number of traditional Guinean plant species used against malaria/fever showed, in addition to their antiplasmodial properties and antimicrobial activity. The fact that some plant species are involved in the traditional treatment of malaria/fever without any antiplasmodial evidence may be justified by their antimicrobial activities.

1. Introduction

Areas of the world with high rates of malaria also carry a heavy burden of infectious diseases which are caused by pathogenic micro-organisms, such as parasites, bacteria, viruses or fungi. Within the poorest and developing countries in Africa, malaria, acute respiratory infections, diarrhea, tuberculosis and recently Ebola figure among the major infectious killers. Although having serious consequences through a prolongation of illness along with an increasing mortality especially to the vulnerable pregnant women and children infected

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with *Plasmodium falciparum*, the magnitude and the impact of malaria co-infection with other pathogenic microorganisms are still largely unknown. Until now, it was suggested that the most important cause of death among children in Africa is malaria; however, the methodology of these studies has been questioned. More recent community-based studies of the incidence of invasive bacterial infections in rural Gambia and Kenya have all documented a significant contribution to childhood morbidity and mortality in developing countries. One of the risk factors to develop invasive bacterial infections in Africa is *Plasmodium falciparum* malaria (Anthony et al., 2009; Scott et al., 2011; Bassat et al., 2009; Bronzan et al., 2007; Church and Maitland, 2014).

In sub-Saharan Africa, concomitant occurrence of malaria and invasive infections by micro-organisms is common. In children with severe *Plasmodium falciparum* malaria, evidence of invasive bacterial infections with Gram-positive *Staphylococcus aureus,* Gram-negative *Escherichia coli,* and other enteric Gram-negative bacteria has been reported in many countries including Tanzania, Kenya, Mozambique, Nigeria and Burkina Faso (Berkley et al., 1999; 2005; Brent et al., 2006; Chaturvedi et al., 2009; Church and Maitland, 2014; Crawley et al., 2010; Evans et al., 2004; Graham et al., 2000; Gwer et al., 2007; Keong and Sulaiman, 2006; Maltha et al., 2014; Uneke, 2008; Walsh et al., 2000). Gram-negative bacteria like *E. coli* may cause amongst others urinary tract infections, pneumonia, neonatal meningitis, diarrhea and skin infections; while Gram-positive organisms like *S. aureus* may cause nosocomial infections, skin infections, respiratory diseases, meningitis, endocarditis, osteomyelitis and wound infections (Gunaselvi et al., 2010).

The major yeasts and fungi implicated worldwide as a potential cause of invasive fungal infections include *Candida* and *Aspergillus* spp. These produce a wide variety of infections that are difficult to diagnose as most of the diagnostic tests are non-specific and the culture takes a long time. *C. albicans* can cause infections in specific physiological and pathological conditions such as infancy, pregnancy, diabetes, prolonged broad spectrum antibiotic administration, steroidal chemotherapy as well as AIDS (Low and Rotstein, 2011). Aspergillosis is one of many opportunistic fungal infections that mainly affect the lungs (Silva, 2010) and 90% of invasive aspergillosis is caused by the air-borne opportunistic fungal pathogen, *Aspergillus fumigatus*. The mortality rate of this disease is still very high (50–95%), partly because of diagnostic difficulties, limited antifungal treatment options, and the weak condition of patients at risk. But also in part because understanding of virulence factors involved in *A. fumigatus* pathogenicity and interactions of the pathogen with the host immune system is still poor (Binder and Lass-Flörl, 2013; McCormick et al., 2010).

Dermatophytic fungal infections are one of the most common infectious diseases and are among the most commonly diagnosed skin diseases in Africa (Nweze, 2010). Although the correlation between malaria and these fungal infections is not documented, they are present worldwide. *Trichophyton rubrum* is responsible for the vast majority of chronic dermatophytoses (Scheers et al., 2013). Its high infectivity and its ubiquitous presence account for its high incidence. Together with the ability of *T. rubrum* to evade host defense mechanisms, this accounts for the high prevalence of infections with this fungus (Dahl and Grando, 1994). Their co-infection with malaria must be common but is poorly documented particularly in malaria endemic areas.

Non-tuberculous mycobacteriosis with *Mycobacterium chelonae* is an opportunistic pathogen which has been recognized as a pulmonary pathogen with increasing frequency. It is an increasingly recognized cause of disease in immunocompromised patients. *M. chelonae* is characterized by a high degree of *in vitro* resistance to antituberculous drugs and has been associated with development of drug resistance and treatment failures. Attempts to eradicate the organism through chemotherapy have been largely unsuccessful. No effective therapy for *M. chelonae* lung infections has been established to date, and reported cases of pulmonary resection for the treatment of *M. chelonae* infections are extremely rare (Singh and Yu, 1992; Green et al., 2000; Goto et al., 2012; Wallace et al., 2001).

Since routine antibiotics along with antimalarials are currently recommended for patients with severe malaria, the indiscriminate use of antibiotics would be both financially costly and could perpetuate the rise of antimicrobial resistance, which threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi (World Health Organization, 2014). Considering the treatment cost of both malaria and microbial infections, along with the level of poverty, most affected African countries are unable to cope with the burden of these diseases. For many African people, particularly the rural populations, traditional medicines continue to be the first and most important source of medical solace when illness strikes health. Thus, many plant species are widely used in the treatment of various diseases as a recipe consisting of only one or more medicinal plants. Moreover, the same plant species or recipe could be frequently and indistinctly employed for the traditional symptomatic treatment of various diseases such as malaria, bacterial and viral infections. In Guinean rural areas where diagnosis based on blood cultures is usually unavailable and antibiotic choice is limited, traditional medicine is the unique way for the management of most of the diseases. Owing to the fact that it is very difficult for traditional healers to differentiate between malaria and other infectious diseases, their remedies mainly aim to treat the fever symptom.

From an ethnobotanical survey on malaria/fever conducted in Guinea, numerous plant species have been collected (Traoré et al., 2013), but only few of them exhibited an *in vitro* antimalarial potency with an $IC_{50} < 64$ μg/ml. To justify the "antimalarial" traditional use of the weakly active or inactive plant species against *Plasmodium falciparum* ($IC_{50} \geq 64$ μg/ml), it was assumed that these could possibly act on symptoms of malaria such as febrile illnesses and/or enhance immunological responses (Traore et al., 2014). Upon these considerations, it is of interest to clarify the biological importance and level of antimicrobial and/or antimalarial activity of the plant species cited by the Guinean traditional healers in the treatment of fever/malaria. Nowadays, a worldwide search for new classes of effective antimalarial and antibacterial drugs is in progress and natural products have been recognized as highly important candidates for such purpose (Tobinaga et al., 2009). Therefore the present study was undertaken.

2. Materials and methods

2.1. Ethnobotanical investigation

The selected plants were collected during an ethnobotanical survey conducted in the four main Guinean regions from May 2008 to September 2010. Botanical identification was first conducted in the field, and confirmed by Dr. S.M. Keita (CERE, University of Conakry), M.S. Barry and N. Camara (Centre de Recherche et de Valorisation des Plantes Médicinales – CRVPM, Dubreka). Voucher specimen registration numbers at the Herbarium of the CRVPM and local names are listed in Traoré et al., 2013. Traditional healers were interviewed in their homes, and herbalists in front of their stalls (on the roadside or on various market places). The questionnaire and oral interviews were based on the standardized model which was designed by CRVPM, Dubreka. The main questions focused on demographic data (age and sex), educational level, professional experience, knowledge about malaria: local names, cause, known signs and symptoms of malaria, plants used in the preparation of antimalarial remedies, plant parts employed, mode of preparation, and mode of administration.

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