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Not ordinary antimalarial drugs: Madagascar plant decoctions potentiating the chloroquine action against *Plasmodium* parasites

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ABSTRACT

Malaria mortality rates have fallen by 47% globally since 2000 and by 54% in the African region, but they are still a major problem. Malaria is caused by *Plasmodium* parasites, vectored to people through *Anopheles* mosquitoes, which mainly bite between dusk and dawn. Currently, a growing number of *Plasmodium* species and strains developed resistance to the most commonly used anti-malarial drugs. Chloroquine (CQ), the most commonly used anti-malarial drug, actually is not effective in a number of cases, and growing *Plasmodium* resistance has been already observed to artemisinin. New approaches are necessary to face this challenge. One of the strategies to overcome the drug resistance in different *Plasmodium* species is the search for compounds known as resistance-modifiers or chemosensitizers. These compounds may restore the CQ sensitivity in CQ-resistant strains of *Plasmodium*. The studies started from the knowledge that some Madagascar populations use decoctions of some local plants in association with low doses of CQ to complement the CQ action against chronic malaria. In such way, resistance insurgence is lowered, as well as collateral effects. Phytochemical analyses on twelve plant species commonly used by local populations to treat malaria evidenced the presence of complex alkaloids, which showed *in vitro* and/or *in vivo* efficacy against CQ-resistant *Plasmodium* strains, attesting the potential use of the mix of CQ and medicinal plant preparations or compounds therein present. The approach, in accordance with recent tendencies on multidrug resistance control, is based on mixtures of natural products and classic antimalarial drugs, with a relevant coincidence between the ethnobotanical reports and the scientific evidence.

Contents

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[2] P. Rasoanaivo, who collaborated to the writing of this manuscript, suddenly died on July 13th 2016. The other authors are presenting this Review as homage to his contribution to ethnopharmacology.

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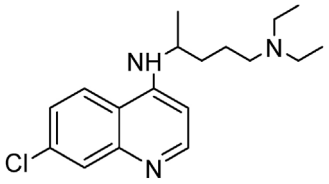
1. Current strategies in the fight against malaria

Mosquito vector-borne diseases pose a major threat to millions of people worldwide. They include malaria, yellow fever, dengue, chikungunya, Japanese encephalitis, St. Louis encephalitis, filariasis and, more recently, outbreaks of Zika virus (Mehlhorn, 2015; Benelli, 2016a,b; Benelli et al., 2016a,b; Ward and Benelli, 2017). Furthermore, Culicidae transmit key pathogens and parasites that dogs and horses are very susceptible to, including the dog heartworm, West Nile virus, and Eastern equine encephalitis (WHO, 2012; Nicoletti et al., 2016a,b; Vadivalagan et al., 2017).

Malaria is a major global health problem. More than 3.4 billion of the world's most vulnerable citizens are at risk of contracting malaria, with about 189 million estimated malaria cases and related 584 000 deaths each year, predominantly among children (WHO, 2014a,b). Among the 109 malaria endemic countries, India had 1.5 million confirmed malaria cases in 2009 with over 1000 deaths (WHO, 2010). Human malaria is caused by *Plasmodium* parasites, vectored to people through the bites of infected *Anopheles* mosquitoes, which mainly bite between dusk and dawn (Benelli, 2015). Most deaths occur among children living in Africa, where a child dies every minute from malaria (Jensen and Mehlhorn, 2009; WHO, 2014a,b). Malaria mortality rates have fallen by 47% globally since 2000 and by 54% in the African region, but they are still a major problem (WHO, 2015). However, this positive trend could be reversed in the next future.

The political and economical stability is getting worst in many parts of Africa, compromising a number of medical treatments. More generally, no part of the world can be considered free from vector-borne diseases (Fradin and Day, 2002). Climate changes are causing the massive migration of alien species and therefore vector-borne diseases are interesting countries so far not involved. Mosquito vectors often showed huge physiological and behavioural plasticity (as recently showed by the Asian tiger mosquito, *Aedes albopictus*) and also experienced a lack of natural enemies, which allow them to invade and become stable in a wide range of new geographical areas (Benelli et al., 2016c; Nicoletti et al., 2016a).

Research should help to give solution to these important global challenges, producing new approaches for novel incoming situations. Concerning prevention and control of the malaria burden, besides the vaccine alternative (Cohen et al., 2012; Benelli and Mehlhorn, 2016), there are two possible approaches to fight malaria: (*i*) combat the diffusion controlling the mosquito vectors, or (*ii*) fight the parasites killing them after the infection. Nowadays, both controls have to face the resistance phenomenon. In this scenario, the control of a growing number of pathogens and parasites is extremely challenging (Nathan and Cars, 2014; Tanwar et al., 2014 Tanwar et al., 2014). On the other hand, mosquito eggs, larvae, and pupae are usually targeted using organophosphates, insect growth regulators, and microbial agents. However, the massive and continuous utilization of chemicals have negative effects on human health and the environment, and induce resistance in a number of mosquito species (Karaagac, 2011; Benelli, 2015; Naqqash et al., 2016). For example, DDT was very efficient against a number of arthropod pests, causing a radical decline of malaria, until it was banned for environmental damages and resistance insurgence (Lima et al., 2011).



Chloroquine

Fig. 1. The structure of chloroquine, the most used antimalarial agent, partially derived from the structure of quina-quina alkaloids.

It is conceivable that, as effect of resistance phenomenon, in the next 20–30 years most of the antibiotics (Sadashiv and Kaliwal, 2016) and pesticides currently in use will lose any efficacy (Lima et al., 2011; Naqqash et al., 2016). The current paradox is that the synthetic substances, extensively employed as pest control tools, are now causing an irreversible catastrophic situation, helping the diffusion and the strength of the vectors and related diseases. Consequently, new approaches are necessary to face this situation, reversing the resistance phenomenon.

The resistance phenomenon plays a key role also in malaria treatment. Chloroquine (CQ) (Fig. 1), firstly synthetized in 1934, is currently the most used anti-malarial drug worldwide. However, the development of CQ-resistant *Plasmodium* strains strongly reduced its effectiveness. After a dominance of synthetic drugs for more than fifty years (Jensen and Mehlhorn, 2009), research is going back to natural products (Benelli et al., 2016d; Alaíde et al., 2009). According to the WHO reports, more than 80% of the total population still needs plants for medicinal treatments (WHO, 2003). It is also important to consider the growing cost of synthetic drugs and the increasing difficulties in their capillary distribution. Also in advanced countries, owing to the collateral effects of synthetic drugs, medicine based on natural products is playing an increasing central role (Nicoletti et al., 2011; Benelli and Mehlhorn, 2016).

Natural products in malaria fight have a long story. In the past, malaria treatment with quinine marked the first successful use of a chemical compound to treat an infectious disease (Achan et al., 2009). The quinine has been originally reported as a component of the bark of the *Cinchona* species (quina-quina tree) from Peruvian highlands, where the trunk bark was employed in traditional medicine against malaria fever. In medicine, it was used to treat malaria from as early as the 1600s, when Jesuit priests first documented its effectiveness. Later on, a series of synthetic drugs, like CQ, structurally derived from quinine four constituents, was considered more effective and therefore worldwide utilized, until the aforementioned resistance phenomenon (Cooper and Magwere, 2007). Therefore, several researchers are looking for plants with active antiplasmodial natural products (Wells, 2011).