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Review

The complexity of medicinal plants: The traditional *Artemisia annua* formulation, current status and future perspectives

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ABSTRACT

Ethnopharmacological relevance: Artemisia annua has a long tradition of use for the treatment of intermittent fevers which we now relate to malarial infections. The active principle artemisinin has been isolated from *Artemisia annua* and today forms the backbone of the global fight against malaria. The traditionally prepared *Artemisia annua* formulation is however still being used on a global scale for the treatment of malaria, and it is claimed that its action is superior to the single purified drug. *Artemisia annua* is therefore on the forefront of the heated debate between the single drug–single target approach of western based medicine and the holistic approach of traditional medicinal systems. This review aims to highlight the complexities we face in the general study of medicinal plants at the hand of three levels of complexity. These levels consist of (a) the chemistry of the medicinal plant, (b) the influence of the preparation method on the chemistry of the final formulation and (c) the influence of metabolism on the chemistry of the formulation. We also aim to provide an up-to-date report on all scientific work that has been conducted and published in English on the traditional formulation of *Artemisia annua.*

Materials and methods: All English scientific literatures published until the first quarter of 2013 were retrieved from well-known scientific databases (Scifinder scholar, Web of Science, PubMed, Google scholar) and Non-governmental organisations active in this field were consulted. A draft version of this manuscript was sent to the African office of the World Health Organisation (WHO), and to the Non-governmental organisations "Action Médicine Naturelle" (ANAMED) and "Iwerliewen fir bedreete Volleker – Réseau belgo-luxembourgeois pour la valorisation des herbes médicinales" (IFBV-BELHERB) for comments.

Results: Very little scientific work has been conducted on the *Artemisia annua* formulation. The available literature contains many discrepancies which are unfortunately selectively being used by the two different sides in this debate to further their arguments. On one side of the argument we have the low content of artemisinin in *Artemisia annua*, the low bioavailability of artemisinin when the traditional formulation is administered and the high levels of recrudescence, which are being emphasised, while on the other side the possible role of synergism and prodrugs are being highlighted. This review reports that there are still too many gaps in our existing knowledge to provide conclusive evidence for either of the two sides of the argument.

Conclusions: Much more research is needed into *Artemisia annua* formulations. We stand to gain invaluable knowledge into how traditional medicinal plant works, discover the identities of new active compounds (which can be used against other diseases such as HIV, diarrhoea, and cancer) and possibly bring both sides of this debate closer together.

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1. Introduction

1.1. Background on the traditional use of Artemisia annua and its implications

Artemisia annua L. (Asteraceae) has been used throughout the ages to treat various ailments, specifically those related to the treatment and prevention of fevers which we now relate to malarial infections. Malaria is a vector-borne infectious disease caused by *Plasmodia* parasites, of which *Plasmodium falciparum* is the most infectious and lethal. *Plasmodium falciparum* infects over 500 million people each year, causing the deaths of more than 1.2 million people and also causes tremendous economic losses in the most affected countries (De Ridder et al., 2008; Murray et al., 2012). The majority of deaths can be attributed to specific high risk groups of which children under five are the most at risk (De Ridder et al., 2008, Willcox et al., 2011).

In ancient China, symptoms relating to *Plasmodium falciparum* infections were effectively treated with the *Artemisia* plant. This history of use is however quite ambiguous as the *Artemisia* plant was referred to as *qing hao* (possibly *Artemisia apiacea* Hance. (Asteraceae)) and *cao hao* (possibly *Artemisia annua*), without sufficient differentiation given between the two species. The differentiation was only provided in the year 1086 when the scholar Shen Gua (1031–1095) noted the differences between *Artemisia annua* and *Artemisia apiacea* (Hsu, 2006, 2010). The ancient preparation method of *Artemisia annua* and *Artemisia apiacea* involved soaking the fresh whole plant in water overnight followed by wringing it out and ingesting the resulting juice or emulsion. A second preparation method has also been discovered in an ancient manuscript and occurs repeatedly in many formulations during the Tang dynasty (618–907). This method involved soaking the entire plant in urine, while it was noted that this preparation method probably decreased contamination with harmful bacteria and increased the extraction efficiency of the active components (Hsu, 2006, 2010). A third method is described in which the plant material is baked on a hot plate until slightly scorched. None of these ancient preparation methods and its influence on the chemical makeup of the final formulation has yet been studied in any detail.

The present day use of *Artemisia annua* to treat malaria is to prepare and consume a tea infusion of the dried leaves of only *Artemisia annua*. The main contradiction between the books from antiquity and the present day use is that historically *Artemisia apiacea* was preferred over the use of *Artemisia annua*. Other discrepancies include that water or urine was used to prepare the formulation at room temperature using the fresh whole plant as opposed to the current practice of preparing a tea infusion of only *Artemisia annua*. These differences in preparation methods can potentially have a big influence on the chemistry of the final formulation. Two excellent reviews on the traditional use of *Artemisia annua* and *Artemisia apiacea* including translations from the ancient Chinese texts were published by Hsu (2006, 2010).

Currently there is renewed interest in using traditional Chinese medicine (Heide, 2006) and future research into the use of *Artemisia annua* and *Artemisia apiacea* can have important implications for antimalarial treatments in developing countries. Especially where other antimalarials may not be readily accessible (Hsu, 2006) or where the high cost of these drugs makes it practically inaccessible to many. Another important factor that is often overlooked is that people in many developing countries do not trust Western based drugs. The reason for this is debatable and the extent of this predicament will be very difficult to measure, however this aspect should not be underestimated. A good example of this lack of trust in Western drugs or where the high cost of these drugs are making it inaccessible, is the recent approval of a prophylactic malaria treatment by the Ugandan government consisting of *Artemisia annua*, lemongrass extracts and ground kernels of avocado, called Artavol. In a recently broadcasted British Broadcasting Cooperation radio interview this was hailed as one of Africa's scientific breakthroughs, together with an electric car, resulting from increased spending on scientific research.

Due to this renewed interest and the growing use of medicinal plants, it is of great importance to study commonly used medicinal plants in detail. The WHO is aware of these issues and intermittently publishes guidelines on the use of specific medicinal plants. In the case of *Artemisia annua* a relatively simplistic view is followed by the WHO and the scientific community active in studying this medicinal plant. In order to reach the prescribed doses of the main active compound artemisinin, they have concluded that Artemisinin Combination Therapies (ACTs) are the best way to approach the treatment of malaria (Mueller et al., 2004; Weathers et al., 2011; WHO, 2012) and that the traditional use of *Artemisia annua* should be discouraged. The ACT treatment regime makes use of artemisinin derivatives in combination with other slower acting antimalarials.

There are however two conflicting opinions. On one side the majority believes that using *Artemisia annua* tea infusions (or the whole plant treatment) will lead *Plasmodium falciparum* to become resistant to artemisinin. This is based on the low levels of artemisinin in *Artemisia annua* leading to difficulties in quality control and standardisation, the low extraction efficiency of water, the low bioavailability of artemisinin if taken in the form of an infusion and the high recrudescence rates in patients using the infusion. The minority view claims that artemisinin is not the only active compound in the infusion and that synergism plays an important role in the overall efficacy. The possible presence of