Monographic study of Terminalia albida used in the treatment of malaria in Guinean traditional medicine: A literature review

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Abstract:
The development of plant monographs commonly used in traditional medicine is an essential element in contributing to the safety of plant use. This review aims to contribute to the elaboration of the monograph of *Terminilia albida*, whose antiplasmodial activities have been demonstrated. A complete review of the literature searching scientific databases covering international peer-reviewed journals was conducted. As search terms, the scientific plant name was used, as such and in combination with "antiplasmodial or antimalarial, pharmacological activity, chemical composition". Data from Doctoral dissertations were also collected.
The macroscopic description focused on the shape, color and arrangement of the leaves, flower and seeds of *Terminalia albida*. For the identification of anatomical elements, microscopic analysis was performed. The results noted the presence of medullary ray and cortical parenchyma in the transverse sections, as well as sclerotic cells and starch grains in the powders of the stems of the plant. Anti-plasmodial, immunomodulatory and anti-oxidant properties have been demonstrated. The phytochemical composition and toxicological data were also reported for a complete monograph of the plant. These data could serve as a basis for the development of an improved traditional drug in the management of uncomplicated malaria in Guinea.

Keywords: *Terminalia albida*, monography, antiplasmodial activity.

Étude monographique de *Terminalia albida* utilisé dans le traitement du paludisme en médecine traditionnelle guinéenne

Résumé :
L'élaboration de monographies de plantes couramment utilisées en médecine traditionnelle est un élément essentiel pour contribuer à la sécurisation de l'utilisation des plantes. Cette revue vise à contribuer à l'élaboration de la monographie de *Terminilia albida*, dont les activités antiplasmodiales ont été démontrées. Une revue complète de la littérature en interrogeant des bases de données scientifiques, couvrant ainsi les revues internationales à comité de lecture, a été réalisée. Comme termes de recherche, le nom scientifique de la plante a été utilisé, tel quel et en combinaison avec "antiplasmodial ou antimalarial, activité pharmacologique, composition chimique". Des données provenant de thèses de doctorat ont également été recueillies.
La description macroscopique a porté sur la forme, la couleur et la disposition des feuilles, des fleurs et des graines de *Terminalia albida*. Pour l'identification des éléments anatomiques, une analyse microscopique a été effectuée. Les résultats ont noté la présence entre autres de rayon médullaire et parenchyme cortical dans les coupes transversales, ainsi que des cellules scléreuses et grains d'amidon dans les poudres des écorces de tige de la plante. Les propriétés anti plasmodiale, immunomodulatrice, anti-oxydante ont été mises en évidence. La composition phytochimique et les données toxicologiques ont été également rapportés pour une monographie complète de la plante. Ces données pourraient servir de base pour le développement d'un médicament traditionnel amélioré dans la prise en charge du paludisme non compliqué en Guinée.

Key words: *Terminalia albida*, monographie, activité antiplasmodiale.

Introduction

Hair Malaria remains a major public health problem in terms of the number of cases and deaths in endemic countries (WHO, 2020; Torto, 2019). The continued exploration of local resources in these countries is an integral part of malaria control strategies due of limited access and the problem of resistance to conventional drugs (Merlin, 2011; Torto 2019).
WHO encourages countries where medicinal plants are widely used by the population to develop plant monographs. These monographs can be based on efficacy, safety and quality control data available in the literature (WHO, 2009).
Moreover, many countries, in the context of the development of traditional pharmacopoeia or the rational use of plants, have defined a framework for writing monographs (Tan et al., 2020; Carvalho et al., 2014). In addition, model plant monographs have been developed and published by WHO to serve as examples. (WHO, 2009; WHO, 2006).

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It is in this perspective that the elaboration of monographs of medicinal plants commonly used was initiated by the Institute of Research and Development of medicinal plants of Guinea. Plants with antimalarial use such as *Terminalia albida* were selected.

Terminalia species have been investigated for their antiplasmodial activity. Interesting antiplasmodial activities have been reported for *Terminalia macroptera, Terminalia mantaly, Terminalia superba, Terminalia avicennioides* (Tchatat Tali et al., 2020; Haidara et al., 2018 ; Ouattara et al., 2014; Mbouna et al., 2018).

The republic of Guinea is endowed with a rich and varied flora that offers great prospects for the discovery of new bioactive molecules. *Terminalia albida* Sc. Elliot (Combretaceae) widely distributed in Guinea, is a plant well known for its ethnomedical reputation in various pathologies including malaria (Traore et al., 2013). Within the framework of the valorization of local resources, the stem barks of *T. albida* have been the subject of numerous scientific investigations both on the ethnotherapeutic and biological levels because of its remarkable efficiency in the treatment of malaria (Camara et al., 2019; Baldé et al., 2021). A remarkable inhibition of the plant has been noted in vitro against the chloroquine resistant strain. Also, in vivo, *T. albida* showed an interesting activity in the treatment of mice infected by two experimental strains *Plasmodium chabaudi* (simple model) and *P. berghei* ANKA (severe model) (Camara et al., 2019).

According to the hypotheses, their composition rich in secondary metabolites such as tannins, terpenes, phenolic acids, flavonoids could justify anti-malarial, immunomodulatory and antioxidant properties already demonstrated (Camara et al., 2019). The objective of this study is to carry out a monograph of *Terminalia albida* based on a literature review on the antimalarial data of this plant. Thus, this work will contribute to the writing of the first national pharmacopoeia in the Republic of Guinea.

Materials and Methods

A complete review of the literature searching scientific databases (Scifinder, Sciencedirect, Google Scholar, PubMed, Web of Science), thus covering international peer-reviewed journals was conducted. As search terms, the scientific plant name was used alone, and in combination with "antiplasmodial or "antimalarial", pharmacological activity, and chemical composition. Data from Doctoral dissertations were also collected.

- ***Botanical study:***

The macroscopic and microscopic studies consisted of a synthesis of the work carried out under the aegis of the Institute of Research and Development of Medicinal Plants of Dubreka and presented in the thesis of Camara (Camara, 2020).

The macroscopic examination focused on the morphological description of the whole plant, i.e. the shape, size, color and arrangement of flowers, leaves, fruits, seeds and stem bark. Microscopic analysis was applied exclusively to the stem bark that constitutes the plant material. Stem bark cross sections were prepared with a sliding microtome (MSE) and stained with Mirande's reagent (carmine-green alum combination) for 2-3 minutes, then washed with water. After staining, the cross sections were mounted on glass slides using glycerol gel. A fine powder of stem bark was mounted on a clean glass slide containing two drops of chloral hydrate at 80 g/20 mL of water (European Pharmacopoeia, 1997).

The slides were observed with a LEICA Microsystems DMLB microscope. Pictures were taken with a CANON Digital Camera Power Shot S40 photo-micrographic system.

Results and Discussion

- ***Nomenclature***

Botanical Nomenclature: *Terminalia albida* Scott-Elliot ;

Synonyms: *T. angyrophylla* Engl. et Diel ;

Botanical Family: Combretaceae ;

Vernacular names in Guinea (Carrière, 2000): Malinke: "Ouolo nidié" ; Poular : "Bori billel "; Soussou : "Cobérafirè".

- ***Definition of the drug***

The drug consists of the dried stem bark of *Terminalia albida* Scott-Elliot.

General distribution: The distribution area of *Terminalia albida* is Western tropical Africa (The International Plant Names Index, 2022).

Distribution in Guinea: T. albida grows in Upper Guinea, Lower Guinea, Middle Guinea, (Lisowski, 2009).

- ***Botanical identification***
  - ***Macroscopic characters of the whole plant***

Botanical investigations are the gold standard for identifying plant species. *Terminalia albida* Scott-Elliot is a savannah shrub up to 12 m high, with a twisted bole and open top, with young, leafy, flowering branches covered with dense, silky, silver hairs (Figure 1). The adult leaves are short-stalked (10 to 20 mm) and alternate; their blade is narrow, lanceolate or oblanceolate, with an acuminate tip that is obtuse or pointed, and a more or less rounded base (Lisowski, 2009). The leaves are 7 to 20 cm long and 2 to 4.5 cm wide. The flowers, grouped by two and surrounded by small bracts (4 mm length), are gathered in raceme, axillary, spiciform, velvety, from 5 to 10 cm length. Fruits are mucronate-tipped elliptical samaras, longer than wide (5.5-6.5 cm long and 2-3 cm wide), with a wing arranged around the seed.

Figure 1: Whole plant of *Terminalia albida* Scott-Elliot (Picture source IRDPMAG).

The stem bark consists of bent elongated fragments is twisted on itself (Figure 2) (Camara, 2020). It is covered with a thick, very scaly, transversely wrinkled and longitudinally cracked cork, sometimes occupying half of the section; the outermost layers exfoliate very easily. This aspect of the bark could be due to the age of the plant, given that age has already been reported as one of the parameters that can impact the quality of a plant (Kiskini et al., 2016). The inner layers of the cork, persistent, have a dark brown appearance, with longitudinal slits and fine transverse wrinkles. When deprived of the cork, the bark has a reddish-brown color on the outside, a smooth, very finely wrinkled appearance longitudinally. The inner surface is yellowish brown to orange brown with darker brown spots and is finely striated longitudinally. The light beige break is fibrous.

Figure 2: Macroscopic view of the stem bark of *T. albida* Scott-Elliot (Camara, 2020)

- ***Microscopic characteristics***

Camara (2000) examinated the cross section of stem bark and showed the following elements: cortical parenchyma, phloem with medullary rays and bundles of fibers, and cambium (Figure 3a). These elements are present in most of the plant kingdom, and ensure the transport of nutrients and water in the plant. The phloem occupies most of the cross section. It is composed of successive layers of parenchyma and bundles of thick-walled lignified fibers (Figure 3b, 3c) (The whole is interrupted with medullary rays (Figure 3b, 3c) composed of thin-walled cells, except for the most external bundles of fibers. At this level, the medullary rays consist either of rounded to ovoid cells, or of long sclereids (Figure 3d). Clusters of calcium oxalate are found in all parenchyma; their size varies from 20 to 400 µm in diameter (Figure, 3e) (Camara, 2020). To date, no clusters of calcium oxalate of such size have been yet reported. The largest size around 100 µm was observed in Combretum fructicosum (Van Vliet, 1979). This specificity could constitute one of the identifying elements of the *T. albida* species in stem bark. Examination powder showed a yellowish-brown color. All the elements, described in the cross-section, were found.

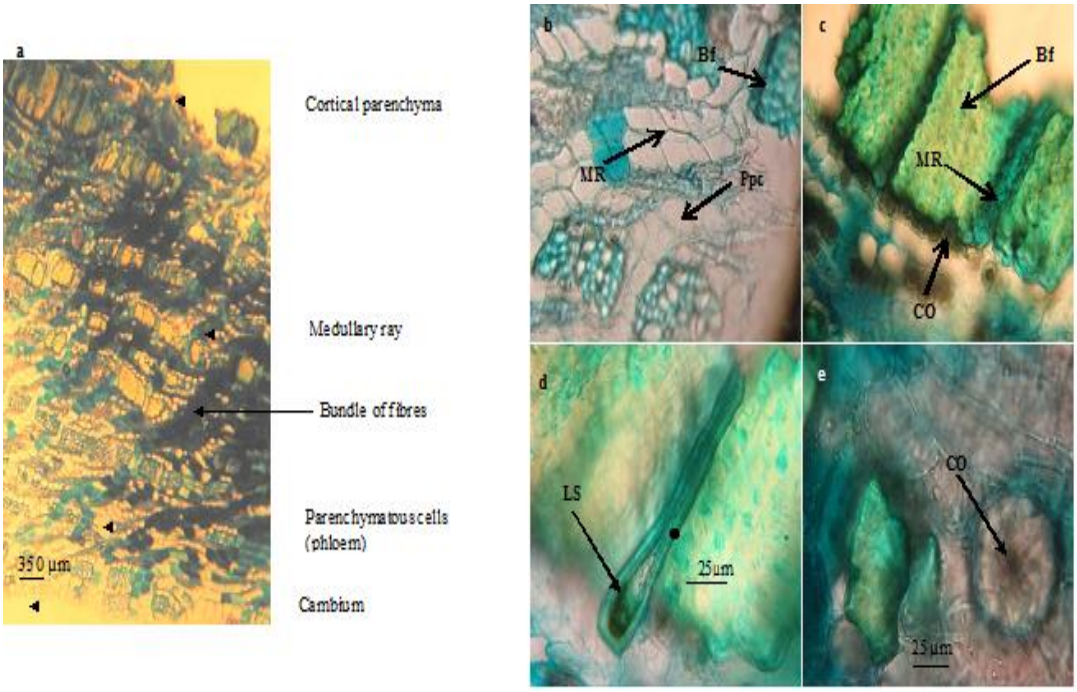

Figure 3: *Terminalia albida* Scott-Elliot: (a) Cross-section of stem bark (without suber) - general appearance, (b, c, d, e) details of the cross section of the stem bark of *T. albida* Scott-Elliot. (Bf): Bundle of fibres; (MR): Medullary ray composed of thin-walled cells; (Ppc): Phloem parenchymatous cells; (LS): Long sclereid between the groups of fibres; (CO): cluster crystal of calcium oxalate (Camara, 2020).

A large number of clusters of calcium oxalate isolated of variable size (Figure 4a) or inserted in the parenchyma (Figure 4b) were observed. Cells from medullary rays or from the external bases of the cortex were small, sclerified, rounded (Figure 4c) or rectangular (Figure 4d) (Camara, 2020).

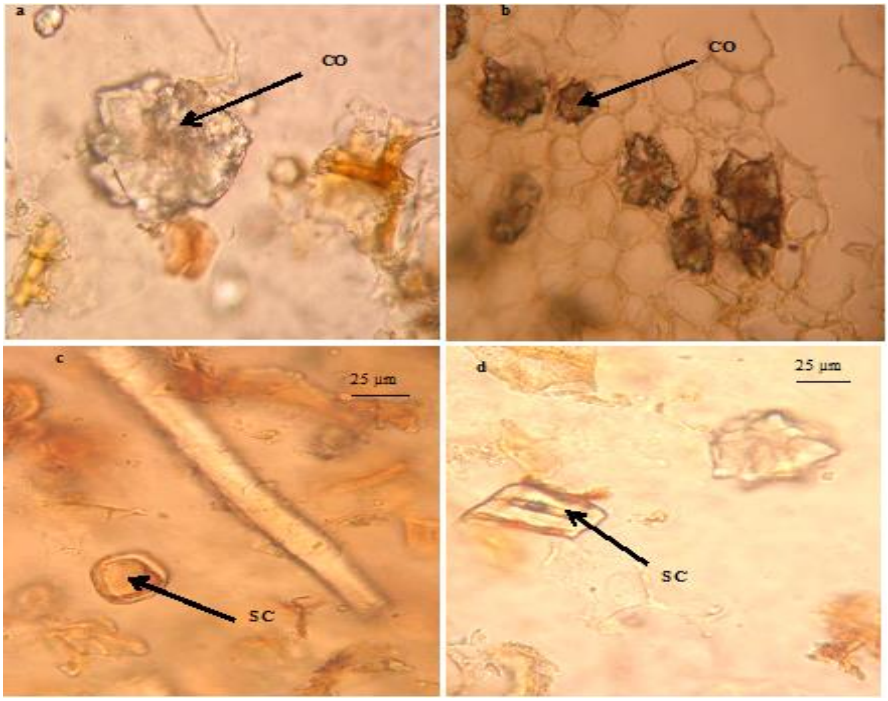

Figure 4: Microscopic view of the stem bark powder of *T. albida* Scott-Elliot. (a, b) CO: calcium oxalate; (c, d) SC: sclerified cells (Camara, 2020).

- ***Traditional uses***

Terminalia albida constitute an important plant in traditional Guinean medicine. Ethnomedical data report that this plant is one of the most used in the traditional management of malaria in Guinea (Traore et al., 2013; Baldé et al., 2020). In addition, in Guinea-Bissau, traditional use of the leaves in the treatment of cough, respiratory diseases, stings, bites and poisoning has been described (Catarino et al.,2016).

- ***Chemical constituents***

Although there is a rich literature on the chemistry of plants in the genus *Terminalia* (Zhang et al., 2019; Das et al., 2020), many of the compounds in the *albida* species remain unidentified. In the traditional recipe valorization program, a recent report showed the presence of hydrolysable tannins, triterpenes, flavonoids, phenol glycosides in the methanolic extract of *Terminalia albida* stem barks (Camara et al., 2019). These compounds, already cited in other *Terminalia* species, constitute the main secondary metabolites of these plants (Das et al., 2020). To date, only the roots have been subjected to extensive chemical analysis by Balde et al. (2021). The authors described the presence of 10 oleanane triterpenoids, among which six new compounds, i.e., albidanoside A, albidic acid A, albidinolic acid, albidienic acid, albidolic acid, and albidiolic acid, and two triterpenoid aglycones, i.e., albidic acid B and albidic acid C in *Terminalia albida* roots (Baldé et al., 2021a; Balde et al., 2021b).

- ***Antiplasmodial activity***

Four studies have reported remarkable antiplasmodial activities of *Terminalia albida* in-vitro extracts on chloroquine-resistant strains of Plasmodium with IC50 between 0.6 and 1.5, 2.4 µg/mL (Traoré et al., 2014, Camara et al., 2019; Balde et al., 2021). These results were confirmed in mice *P. berghei*-infected treated with polar extracts of stem bark (Camara et al., 2019). *Terminalia albida* treatment signifcantly decreased parasitaemia by 89% on Day 7 post-infection (Camara et al., 2019). Bioguided fractionation showed significant in vitro actiplasmodial activity of pantolactone isolated from the dichloromethane extract of *T. albida* roots (Balde et al., 2021a).

There are few studies on the pharmacological effects of *T. albida*. The work carried out by Camara et al. (2019) demonstrated an effect of *T. albida* extracts, in addition to its potential antiparasitic effect, on the survival of mice infected with the experimental model of *P. berghei* ANKA brain malaria. This activity could be justified by blocking the imbalance of the immune system due to the sequestration of parasitized red blood cells in the cerebral microvascular system (Newton et al., 2000). Indeed, malaria pathogenesis can lead to simple non-lethal malaria or cerebral malaria; responsible for 15-20% of deaths worldwide mainly in sub-Saharan Africa (Ghazanfari et al., 2018; Rénia et al., 2012).

On the other hand, metholic extracts led to significant inhibition of TNF, IL-1β, IL-6, and IL12 expression in mice, four pro-inflammatory cytokines (Camara et al., 2019).

- ***Toxicity of Terminalia albida***

The data in the literature only report the acute toxicity of *T. albida*.

T. albida stem bark administration to C57BL/6 mice at a dose of 2000 mg/kg did not cause mortality or major behavioral changes among experimental animals during the 20 days of tracking (Camara et al., 2019). Mice body weight was not modified by the administration of *T. albida.* Thus, LD50 of *T. albida* is greater than 2000 mg/kg in C57BL/6 mice (Camara et al., 2019). These preliminary results seem to demonstrate the non-toxicity of the stem bark of this plant.

Conclusion

This study made it possible to collect data on macroscopic and microscopic characteristics, on toxicology, on antiplasmodial and chemical composition of *T. albida*. However, additional studies, especially on the pharmacological and clinical surveys are necessary to reinforce the validation of this specie as a plant candidate for malaria treatment. Acknowledgment: The research work carried out by our team and cited in this work was essentially funded by the Ministry of Higher Education and Scientific Research of Guinea and in part by the Embassy of France in Guinea. We thank them in particular for the financing of the botanical study.

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