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ANTIPLASMODIAL ACTIVITY OF THE ETHANOLIC EXTRACT OF *ICACINA OLIVIFORMIS* (STEMS), *SPONDIAS PURPUREA* L.(LEAVES, BARKS AND ROOTS) AND *COCOS NUCIFERA* L. (COCONUT SHELL FIBERS) FROM ZIGUINCHOR, SENEGAL

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ABSTRACT
Icacina oliviformis (poiret) Raynal (Icacinaceae), *Spondias purpurea* L. (Anacardiaceae) and *Cocos nucifera* L. (Arecaceae) are Senegalese traditional pharmacopoeia plants used in the treatment of various diseases. These plants are used in the treatment of malaria and related conditions in south Senegal. To establish its efficacy, the ethanolic extract was investigated. This prompted us to assess their antiplasmodial activity against the chloroquine-sensitive 3D7 and chloroquine-resistant W2 strains of P. *falciparum* as well as their cytotoxic activity against HUVEC cells. The *Icacina oliviformis* extract revealed antiplasmodial activity (IC50 <1µg/mL) with no toxicity (CC50 >100). The antiplasmodial activity and the toxicity of the stems of *Icacina oliviformis*, *Spondias purperea* (leaves, barks, and roots) and *Cocos nucifera* (coconuts shell fibers) are reported for the first time. The ethanol fraction of *Icacina oliviformis* stems showed stronger antiplasmodial activity than the other extracts.

KEYWORDS: *Icacina oliviformis, Spondias purpurea* L., *Cocos nucifera* L., *in vitro*, P. *falciparum*, antiplasmodial.

1. INTRODUCTION
The number of cases of malaria and associated deaths was estimated at 212 million and 429 000 worldwide.[1] The WHO region remains the most affected, with about 90% of malaria cases and 92% of all deaths in 2015.[1] The most serious manifestations of malaria are caused by Plasmodium *falciparum*. Antimalarial drug resistance has emerged as one of the strongest challenges presently facing malaria control in developing countries. The situation has worsened because malaria parasites are becoming resistant to several antimalarial agents.[2,3] Medicinal plants have been used in almost all cultures as a source of medicine.[4,5] With the aim of discovering new natural active extracts against malaria parasites, *Icacina oliviformis*, *Spondias purpurea* and *Cocos nucifera* were selected after an ethnopharmacological survey conducted on plants used in the traditional treatment of malaria in Senegal. *Icacina oliviformis* is mostly found in west and central Africa.[6,7] The leaves and root bark are used as antihyperglycemia, antimalarial, and antimicrobial.[8,13] The Spondias genus consists of 18 species distributed in tropical and subtropical areas worldwide, with 9 species occurring in the Neotropics.[14] In addition to the use of Spondias fruits in the food industry, some species have also been used as medicinal plants, such as *Spondias purpurea*, which has experimentally demonstrated antioxydant and antifungal effects.[15,16] *Cocos nucifera* (L.) (Arecaceae) is commonly called the "coconut tree" and is the most naturally widespread fruit plant on Earth. Throughout history, humans have used medicinal plants therapeutically. Minerals, plants, and animals have traditionally been the main sources of drugs. The constituents of *Cocos nucifera* have some biological effects, such as antihelminthic, antiplasmodial, antiinflammatory, antinociceptive, antioxidant, antidiabetic, antifungal, antimicrobial, and antitumor activities.[17,19] The objective of this study was to : i) fractionate stems compounds of *Icacina Oliviformis*, leaves, barks and roots of *Spondias purpurea* and coconut fibers with solvents of different polarities, ii) test fractions obtained on chloroquine sensitive 3D7 and chloroquine-resistant W2 strains of P. *falciparum* as well as their cytotoxic activity against HUVEC (Human

Umbilical Vein Endothelial Cells). For the first time, we report a study of antiplasmodial activity performed on *Icacina oliviformis* (stems), *Spondias purpurea* (leaves, barks and roots) and *Cocos nucifera* (coconut schell fibers) extracts.

2. MATERIALS AND METHODS

2.1 Plants Materials

Stems of *Icacina oliviformis*, leaves, barks and roots of *Spondias purpurea* L. and coconut fibers of *Cocos nucifera* were collected in April 2016 from kandé quarter, region of Ziguinchor, Senegal. The plants were authenticated by Prof. E. Bassène, Pharmacognosy and botany Department, University Cheikh Anta Diop, Dakar, Senegal. Voucher specimens were deposited at the herbarium the Pharmacognosy and botany laboratory under respective numbers 2016/021, 2016/022 and 2016/023.

2.2 Plants extraction and fractionation

The samples are dried in the shelter of sun's rays at the ambient temperature of the laboratory (30°C). The dried drugs are crushed using a grinder (type Bradender OHG Duisburg). The fine powders (250 g) thus obtained after spraying were used as raw material to make the extractions. Successive depletion of the powder is achieved by solvents of increasing polarities (cyclohexane, dichloromethane, ethanol, and water). Indeed 250g of powder of each sample are introduced into a 5 L flask containing 3 L of solvent and then refluxed for 4 hours. The ethanolic extracts were evaporated to dryness to give a residue of mass *Icacina oliviformis* (stems), *Spondias purpurea* (leaves, barks and roots) and *Cocos nucifera* (coconut schell fibers) (Table I).

2.3 Phytochemical methods

Phytochemical screening of secondary constituents present in the plant extracts was carried out using methods adopted in similar surveys.[20] This quantitative and phytochemical analysis of these plants was determined as follows: Sterols and terpenoids (Lieberman's reagents); alkaloids (Bouchardat's / Valser-Mayer's / Dragendorff's reagents); flavonoids (concentrated HCl + magnesium ribbon); tannins (Stiasny's reagent, $FeCl_3$ test); saponins (foaming test); free or combined quinone substances (Borntraegen's reagent).

2.4 Antiplasmodial assay

The antimalarial activity of extracts/compounds was evaluated against *P. falciparum* 3D7 and *P. falciparum* W2 strains, using the fluorescence-based SYBR Green I assay approach in 96-well microplates as described by Smilkstein and al.[21] with some modifications. Positive control wells for each assay contained no inhibitor while negative controls contained Chloroquine (CQ). The CQ molecule was provided from World Wide Antimalarial Resistance Network (wwarn Network). Experiments were run in duplicate with both test and control drugs employed at varying concentrations. Stock solutions (extracts) were prepared in dimethyl-sulfoxide (DMSO) and diluted with culture medium to give a maximum DMSO concentration of 0.5% in a final well volume of 200 µL containing 1% parasitemia and 2.5% haematocrit. Extracts and negative control [Chloroquine (CQ)] were prepared by two-fold dilution, in a dose-titration range of 0.098-100 µg / mL, to obtain 11 concentrations each, in duplicate. The concentrations used for CQ were between 0.5 and 1000 nM. After 48 h incubation, the plates were subjected to 3 freeze thaw cycles to achieve complete hemolysis. The parasite lysis suspension was diluted 1:5 in SYBR Green I lysis buffer (10 mM NaCl, 1 mM Tris HCl pH8, 2.5 mM EDTA pH 8, 0.05% SDS, 0,01 mg/mL proteinase K and 10X SYBR Green I). Incorporation of SYBR Green I in parasite DNA amplification was measured using the Master epRealplex cycler® (Eppendorf, France) according the following program to increase the SYBR green incorporation: 90°C for 1 min, decrease in temperature from 90°C to 10°C for 5 min with reading the fluorescence 10°C for 1 min and a new reading at 10°C for 2 min. The IC_{50} was calculated by nonlinear regression using icestimator website 1.2 version: http://www.antimalarial-icestimator.net/MethodIntro.htm.

2.5 Cytotoxicity on HUVEC

HUVEC cells were cultured in Gibco™ RPMI 1640 medium (Life technologies, France) complemented with 10% Fetal Bovine Serum and 1 mM L-glutamine (Sigma-Aldrich, France) and incubated in 5% CO_2 at 37°C. The cytotoxicity of extracts was evaluated using the SYBR Green I assay as previously described. HUVEC were seeded in a 96-well plate at 100,000 cells/well and incubated for 24h to adhere. After discarding the old medium, the cells were incubated in the medium containing eight concentrations (0.78-100 µg/mL) of each extract in duplicate. After 48h incubation, cells were visualized using an inverted microscope to check their morphology or the cell viability. The medium was subsequently removed and replaced by lysis buffer without SYBR Green I and the plates were subjected to 3 freeze-thaw cycles. The cell lysis suspension was diluted 1:2 in SYBR Green I lysis buffer. The incorporation of SYBR Green I in cell DNA and the IC_{50} analysis were obtained as previously.

3. RESULTS

The Table 1 gives the yields of the different fractions obtained. The yield is calculated as being the ratio of the mass of the extract on that of the starting dried powder.

Tableau 1: Extraction Yields.

Extracts	weight(g)	yields (%)
Stems ethanolic of *Icacina oliviformis* (SIS)	2.7	1.1
Leaves ethanolic of *Spondias purpurea* (LSP)	20.71	8.3
Bark ethanolic of *Spondias purpurea* (BSP)	17.26	6.9
Root ethanolic of *Spondias purpurea* (RSP)	7.69	3.07
Fibers shell coconut (FCN)	22.86	6.9

Table 2: Phytochemical screening results.

Extracts	Sterols and polyterpenes	Polyphenols	Flavonoids	Tannins	Alkaloids	Saponins
SIS	+	-	-	-	+	-
LSP	+	+	+	+	+	-
BSP	-	+	+	+	+	-
RSP	+	+	+	+	+	-
FCN	+	+	+	+	+	+

+ : positive reaction
- : negative reaction

After extraction, ethanolic extracts were tested on chloroquine sensitive 3D7 and chloroquine-resistant W2 strains of P. *falciparum* as well as their cytotoxic activity against HUVEC. The test results are shown in Table 2.

Table 3: **Antiplasmodial activity, cytotoxicity and selectivity indexes of fractions SIS, LSP, BSP, RSP and FCN.**

	Extracts	Plasmodium falciparum 3D7 strain	Plasmodium falciparum W2 strain	HUVEC cells
		IC50 μg/mL ± SD	IC50 μg/mL ± SD	CC50 μg/mL ± SD
1	SIS	9.71 ± 2.26	0.16 ± 0.03	>100
2	LSP	29.85 ± 5.31	15.92 ± 4.49	>100
3	BSP	12.34 ± 1.83	34.08 ± 5.31	>100
4	RSP	6.77 ± 1.05	13.62 ± 3.64	>100
5	FCN	11.24 ± 3.81	>100	>100
6	CQ	5.92 ± 0.21	38.71 ± 1.46	>100

CQ = Chloroquine.

5. DISCUSSION

This study describes the extraction of *Icacina oliviformis* (stems), *Spondias purpurea* L. (leaves, barks and roots) and *Cocos nucifera* L. (coconut shell fibers) and the examination of their antiplasmodial activities (Table 3). We retain in the table 1 that the leaves, barks of *Spondias Purpurea* and coconut shell fibers of *Cocos nucifera* are very rich in polar compounds.

The P. *falciparum* 3D7 strain (chloroquine-sensitive) and W2 strain (chloroquine-resistant) strains used gave, with chloroquine, IC_{50} of 5.92 ± 0.21 µg/mL and 38.71 ± 1.46 µg/mL respectively. According to the WHO recommendations and previous works[22,25], antiplasmodial activities of plant extracts were classified as follows: highly active extracts with IC_{50} <5 µg/mL, promising activity at 5-15µg/mL, moderate activity at 15-50 µg/mL and inactivity at > 50 µg/mL. On the basis of its WHO recommendations, we can say that the results of the four extracts are in the range of very high to moderate activities. Thus, SIS, BSP, RSP and FCN extracts are promising and LSP is moderate on P. *falciparum* 3D7 strain. The activity with the P. f*alciparum* W2 strain (chloroquine-resistant) is: inactive FCN, moderate BSP and LSP, promising RSP and very high SIS. The extract SIS gave a best antiplasmodial activity on the P. *falciparum* W2 strain (chloroquine-resistant) (IC_{50}=0.16 ± 0.03µg/ mL). The IC_{50} of SIS on P. *falciparum* W2 strain (0.16µg/ mL) was lower than that on P. *falciparum* 3D7 strain. This shows that there is no correlation between IC_{50} value obtained with SIS and the chloroquine-sensitivity of the strain tested. This phenomenon was described by several authors testing antiplasmodial activity of natural products.[26,28]

Phytochemically, a chemical characterization of *Icacina oliviformis* showed the presence of alkaloids, sterols and terpenes*; Spondias purpurea*: polyphenol, flavonoids, tannins, alkaloids, sterols and polyterpenes, *Cocos nucifera*: polyphenol, flavonoids, tannins, alkaloids, sterols, polyterpenes and saponins (Table 2). Several studies have described the antiplasmodial effect of these secondary metabolites[29,35] which could explain the observed results on the activity of extracts of *Icacina oliviformis*, *Spondias purpurea* and Coconut shell fibers.

Many plants belonging to other traditional medicines gave active extracts and very active purified molecules against P. *falciparum* strains. Nevertheless, the results of this study can be compared to those of known antiplasmodial plants such as *Nauclea latifolia* (stem

bark, IC_{50} of 1.7 ± 0.3 µg/mL)[36] and *Icacina oliviformis* (leaves, IC_{50} of 0.9 ± 0.06 µg/mL).[6]

The traditional use of *I. oliviformis* for the treatment of malaria could be attributed to the presence of certain phytochemicals compounds that constitute the bioactive principles. Numerous medicinal plants containing a wide variety of secondary metabolites have shown antiplasmodial activities.[37,38] The extract of the stems of *I. oliviformis* showed a strong inhibition on the P. *falciparum* W2 strain. However, for the other extracts we will note promising or moderate inhibitions depending on the strain nature of P. *falciparum*. These findings support the ethnomedical use of these plants in the treatment of malaria and associated symptoms.

4. CONCLUSION

The antiplasmodial activity of the stems of *Icacina oliformis* has shown promising results in the field of malaria research. The results of the present study have shown that the ethanol rootbark extract of *I. oliviformis* possesses potent antiplasmodial activity and may therefore serve as potential sources of effective and affordable antimalarial agents. Therefore, this study provides a molecular basis to justify the use of these plants in Senegalese traditional medicine.

Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content of this manuscript.

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