

# Antioxidant and Antiplasmodial Activities of Extracts from *Gardenia erubescens* Stapf et Hutch. and *Fadogia agrestis* Schweinf. ex Hiern. (Rubiaceae)

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## Abstract

Two medicinal plants, *Gardenia erubescens* and *Fadogia agrestis* were selected to evaluate their biological activities. Their total phenolic and flavonoid contents were assessed using folin-ciocalteu and aluminum chloride reagents' methods. The antioxidant activity was estimated using DPPH (1,1-diphényl-2-picrylhydrazyl), ABTS (2,2'-azinobis-[3-ethylenthiazoline-6-sulfonic acid]) and FRAP (ferric reducing antioxidant power). The antiplasmodial activity of the extracts was determined *in vivo* on 42 NMRI mice. The results indicate that all the extracts from both two plants contain some polyphenols. The ethanolic extract of the leaves of *Gardenia erubescens* showed the best antioxidant activity by the method of DPPH. The aqueous extracts of the leaves of *Gardenia erubescens* and the whole plant of *Fadogia agrestis* have a reducing power similar to control (quercetin). All the extracts have a low capacity to scavenge the ABTS radical cation compared to the controls (trolox and quercetin). Concerning the antiplasmodial activity, all the extracts presented moderate antiplasmodial activities. This result could justify the traditional uses of *Gardenia erubescens* and *Fadogia agrestis* to treat of malaria in Burkina Faso.

## Keywords

Antiplasmodial Activity, Antioxidant Activity, *Gardenia erubescens*, *Fadogia agrestis*

## 1. Introduction

Malaria is a public health problem around the world [1] [2]. In 2018, there are estimated 228 million cases and 405,000 malaria deaths worldwide, and 94% of these deaths occur in Sub-Saharan Africa. In South Asia and Africa, malaria continues to affect pregnant women and children more strongly with around 80% of deaths in pregnant women and children under 5 years [3]. In Burkina Faso, malaria remains the leading cause of morbidity and mortality with 3,501,245 cases and 1002 deaths [4]. It remains the primary reason for consultation in health facilities. For the treatment of this disease, WHO recommends artemisinin-based combination therapy (CTA) for uncomplicated malaria caused by *P. falciparum*. For severe malaria, it is preferable to use injectable artesunate (intramuscularly or intravenously) for 24 hours followed by a complete CTA of 3 days once the patient can tolerate oral medications [5]. However, the treatment of this erythrocytopathy leads more and more problems with the resistance of the parasites to the usual antimalarial drugs, such as artemisinin and its derivatives [6] and anopheles to insecticides [7]. This resistance problem has sparked a renewed interest in traditional medicine [8]. The medicinal plants constitute a source of molecules of therapeutic interest [9] which can contribute to the development of new molecules which are both effective and accessible to the poorest populations, the main and vulnerable target of malaria. Many molecules namely quinin and artemisinin used in therapeutics are from plant origin [10]. A previous study has shown that the aqueous extract of *Fadogia agrestis* (*F. agrestis*) has an antiplasmodial activity *in vitro* and an IC<sub>50</sub> of  $4 < IC_{50} < 10$  g/ml [11]. Regarding *Gardenia erubescens* (*G. erubescens*), the ethanolic extract of the barks has an antioxidant activity [12]. These results prove that studies have been done on these 2 species but concerning their *in vivo* antiplasmodial activity. This is how the present work, although preliminary, was initiated in order to determine the antiplasmodial and antioxidant activities of the ethanolic and aqueous extracts of *Gardenia erubescens* and *Fadogia agrestis*.

## 2. Material and Methods

### Plants materials

The leaves, barks (trunk) of *G. erubescens* and the whole plant of *F. agrestis* were collected in September 2019 in the classified forest of Dinderesso, a village located about 15 km and west of Bobo-Dioulasso (second city in Burkina Faso after Ouagadougou). The plants were identified by Dr Harmane Ouoba, a botanist-cytoecologist from Université NAZI BONI (UNB).

### Female albino mice

The mice used are female albino mice of NMRI (Naval Medical Research Institute) strains with an average weight of  $25 \pm 3$  g and 2 months old. These mice were purchased from the animal husbandry of the International Center for Research and Development on Livestock in Subhumid Zones (CIRDES) in Bobo-Dioulasso. They had access to a standard pellet diet and water *ad libitum*.

### ***Plasmodium berghei***

*Plasmodium berghei* (strain ANKA) is continuously maintained in the entomology laboratory of Health Sciences Research Institut at Bobo-Dioulasso by an acyclic passage from infected mice to healthy mice through an injection of parasitized blood.

## **3. Extracts Preparation**

### **Preparation of aqueous extracts**

Decoctions were performed by adding to 500 mL of distilled water to the sample (50 g), heated and boiled under reflux for 15 min. The decoctions were frozen and lyophilized.

### **Preparation of ethanolic extracts**

The plant samples (20 g) were sequentially extracted with 200 ml of petroleum ether and ethanol using a soxhlet apparatus. The extracts were first concentrated to maximum using soxhlet dispositive and then to dryness at room temperature in the Petri dishes.

## **4. Determination of Total Phenolics and Total Flavonoids**

**Total phenolics:** Total phenolics were evaluated according to the colometric method described by Meda *et al.* in [13]. To 0.125 ml of the sample solution was added 0.625 ml of Folin-ciocalteu reagent (FCR 0.2N) and the whole was incubated in the dark for 5 minutes. 0.5 ml of sodium carbonate (75 g/L) was then added to the mixture and incubated again for 2 hours in the dark. The absorbances were read at 760 nm against a standard gallic acid curve ( $y = 4668e-3 * x - 0.034$ ,  $r^2 = 0.9991$ ). A series of 3 tests were carried out for each extract, then the average of 3 measurements was calculated. The results are expressed in mg of gallic acid equivalent per 100 milligrams of the extract (mg EAG/100mg).

**Total flavonoids:** Total flavonoids were assessed by the aluminum chloride method [13]. 0.625 ml of the sample solution was mixed with 0.625 ml of 2%  $AlCl_3$ . After waiting 10 minutes in the dark, the absorbances were read at 415 nm using a quercetin calibration curve ( $Y = 1.259e-02 * x$ ;  $r^2 = 0.9990$ ). A series of 3 tests were carried out for each extract; then the average of the 3 measurements was calculated. The results were expressed in mg of quercetin equivalent (QE)/100mg of the extract.

## **5. Evaluation of Antioxidant Activity *in Vitro***

The antioxidant power of the ethanolic and aqueous extracts of plants was achieved by 3 methods: the scavenging of the free radical (DPPH), the scavenging of the cation radical (ABTS) and the reduction of ferric chloride (FRAP).

**DPPH (2,2-diphenyl-1-picrylhydrazyl):** The antioxidant activity was evaluated by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method as described by [14]. A series of cascade dilutions of the initial solution (10 mg/ml) was carried out for each extract. In each tube a volume of 0.375 ml of the sample solution was mixed with 0.75 ml of the DPPH solution (20 mg/l) and the whole is incu-

bated for 15 minutes in the dark. The absorbances are read at 517 nm and methanol is used as the blank sample. The antioxidant activity is expressed as a percentage of inhibition according to the following formula: % inhibition = (White absorbance – Sample absorbance)/white absorbance × 100%. Three readings are taken per extract and the average of the IC<sub>50</sub> (concentration causing 50% inhibition of the DPPH radical) determined graphically, is calculated.

**ABTS (2,2'-azinobis-[3-ethylthiazoline-6-sulfonic acid]):** The ABTS method was carried out according to the method described by [13]. The cation radical ABTS<sup>•+</sup> was regenerated by mixing an aqueous solution of ABTS (7 mM) with 2.5 mM potassium persulfate (final concentration) and the mixture is kept in the dark at room temperature for 12 hours before use. The mixture was then diluted with ethanol to give an absorbance of 0.70 ± 0.02 at 734 nm using the spectrophotometer. 10 µl of the sample solution was added to 990 µl of the ABTS reagent and the whole is incubated for 15 minutes, protected from light. The absorbances were read in a spectrophotometer at 734 nm against a standard curve of ascorbic acid. A series of 3 tests were carried out for each extract, then the average of the 3 measurements was calculated. The results were expressed in µmol equivalent ascorbic acid per 1 gram of extract (µmol EAA/g of extract).

**FRAP (Ferric Reducing Antioxidant Power):** The reducing power by the FRAP method was determined according to the method described by [13]. The sample solution (0.250 ml) was mixed with 0.625 ml of the phosphate buffer solution (0.2 M; pH 6.6) and 0.625 ml of potassium hexacyanoferrate (1%). The whole was incubated at 50°C for 30 minutes in a sonicator. After incubation, 0.625 ml of trichloroacetic acid (10%) was added and the mixture was centrifuged at 3000 rpm for 10 minutes. After centrifugation was completed, 0.3125 ml of the supernatant was added to 0.3125 ml of distilled water and 0.0625 ml of freshly prepared iron chloride (0.1%). The absorbances were read at 700 nm against a standard curve of ascorbic acid ( $y = 3,270e-3 * x, r^2 = 0.9990$ ). A series of 3 readings was carried out and the reducing power was expressed in µmol ascorbic acid equivalent for 1 gram of extract (µmol EAA/g of extract).

## 6. Determination of Antiplasmodial Activity *in Vivo*

This activity was carried out according to the protocol described by [15]. Seven groups of six mice including six test groups and one control group were used to carry out this test.

**Mouse infestation:** On D<sub>0</sub>, 10<sup>7</sup> parasitized erythrocytes, obtained by dilution of parasitized blood from mice infested with *P. berghei* ANKA were administered intraperitoneally to the groups of mice. The volume of parasitized blood to be injected into each mouse was 200 µL.

**Mouse treatment:** 2 hours after the infestation, the mice except the control group receive orally, the dose of extract (250 mg/kg) intended for the group and the control group receives the dilution solution of the extract (distilled water). The dose is administered once a day for 4 successive days from D<sub>0</sub> to D<sub>3</sub>. The mice were observed during these 4 days to note any changes in behavior that

may occur during treatment.

**Fixing - staining and reading of slides:** On D<sub>4</sub>, blood smears were taken with the blood collected at the tail of the mice. Thin smears are fixed with methanol, dried and then stained with 10% Giemsa solution for 10 minutes and then examined under an optical microscope (100× objective). The parasitemia of each slide is obtained by the median of the results of the reading of three fields containing 100 red blood cells. An average of three readings by different people was done.

**Statistical analysis:** The data in the tables are expressed as an average ± standard deviation (SD). Statistical analysis was performed (calculation of means, standard deviations and P values) with software R. The graphs were constructed with Excel 2019.

## 7. Results

### Determination of Total Phenolics and Total Flavonoids

**Total phenolic contents:** The results of the phenolic contents were as shown in **Table 1**. The total phenolic contents of the leaves and barks of *G. erubescens* varied from  $15.42 \pm 2.78$  to  $36.06 \pm 5.52$  mg EAG/100mg extract. However, ethanolic extract from the leaves ( $36.06 \pm 5.52$  mg EAG/100mg extract) had a better total phenolic content compared to aqueous extract ( $26.28 \pm 1.94$  mg EAG/100mg extract). As for the bark, no significant difference was observed between total phenolic content of ethanolic extract and that of aqueous extract. Regarding *F. agrestis*, no significant difference was observed between the total phenolic content of aqueous extract ( $13.21$  mg EAG/100mg extract) and that of ethanolic extract ( $12.42$  EAG/100mg extract).

**Total flavonoid contents:** The total flavonoid contents of the leaves and barks of *G. erubescens* varied from  $2.62 \pm 0.07$  to  $4.05 \pm 0.23$  mg EQ/100mg of extract (**Table 2**). There was no significant difference between the total flavonoid contents of ethanolic extract ( $3.36 \pm 0.09$  mg EQ/100mg of extract) and aqueous one ( $4.05 \pm 0.23$  mg EQ/100mg of extract) of the leaves of *G. erubescens*. The same trend was found with ethanolic extract ( $2.62 \pm 0.07$  mg EQ/100mg of extract) and aqueous one ( $3.62 \pm 0.56$  07 mg EQ/100mg extract) of the bark of *G. erubescens*. Concerning *F. agrestis*, there was a significant difference between the total phenolic content of ethanolic extract ( $4.10 \pm 0.12$  mg EQ/100mg of extract) and that of ethanolic extract ( $4.95 \pm 0.12$  mg EQ/100mg extract) with P-value= 0.01905.

## 8. Evaluation of Antioxidant Activity *in Vitro*

### DPPH(2,2-diphenyl-1-picrylhydrazyl)

In **Figure 1**, the IC<sub>50</sub> of the various plant extracts evaluated by the DPPH method varied from 2.21 to 27.43 µg/ml. Of all the extracts, the aqueous extract from the bark of *G. erubescens* had the highest IC<sub>50</sub>. However, with the exception of the aqueous extract of the leaves of *G. erubescens* all extracts had IC<sub>50</sub>

higher than those of the two controls (quercetin and trolox). However, only the aqueous extract of the leaves of *G. erubescens* had an  $IC_{50}$  similar to that of trolox (control). In view of these results, only the aqueous extract of the leaves of *G. erubescens* has a good antioxidant activity by the DPPH method.

**Table 1.** Total phenolics of aqueous and ethanolic extracts of Whole plant of *F. agrestis*, leaves and bark of *G. erubescens*.

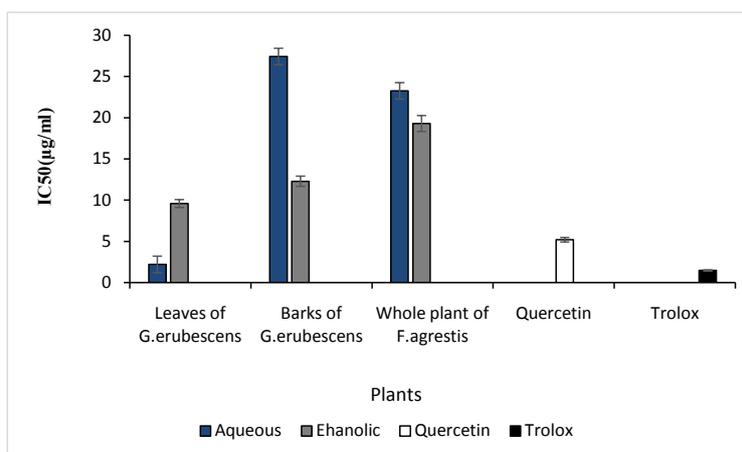
Plants	Extracts	Total phenolics (mg EAG/100mg of extract)	P-value
Leaves of <i>G. erubescens</i>	Ethanolic	36.06 ± 5.52	0.01363 *
	Aqueous	26.28 ± 1.94	
Barks of <i>G. erubescens</i>	Ethanolic	15.42 ± 2.78	0.14
	Aqueous	21.85 ± 2.63	
Whole plant of <i>F. agrestis</i>	Ethanolic	12.42 ± 0.98	0.99
	Aqueous	13.21 ± 0.61	

Comparison between the total phenolics of aqueous and ethanolic extracts from leaves, barks and whole plant of *Gardenia erubescens* and *Fadogia agrestis*. Values were Mean ± standard deviation (n = 3). P-value \*: difference was significant.

**Table 2.** Total flavonoids of aqueous and ethanolic extracts of Whole plant of *F. agrestis*, leaves and bark of *G. erubescens*.

Plants	Extracts	Total flavonoids (mg EQ/100mg of extract)	P-value
Leaves of <i>G. erubescens</i>	Ethanolic	3.36 ± 0.09	0.06
	Aqueous	4.05 ± 0.23	
Barks of <i>G. erubescens</i>	Ethanolic	2.62 ± 0.07	0.00562 **
	Aqueous	3.62 ± 0.56	
Whole plant of <i>F. agrestis</i>	Ethanolic	4.10 ± 0.12	0.01905 *
	Aqueous	4.95 ± 0.12	

Comparison between the total flavonoids of aqueous and ethanolic extracts from leaves, barks and whole plant of *Gardenia erubescens* and *Fadogia agrestis*. P-value \*: difference was significant, P-value \*\*: difference was very significant.



**Figure 1.** Antioxidant activity of aqueous and ethanolic extracts of leaves and bark of *G. erubescens* and of the whole plant of *F. agrestis* by the method of DPPH.

### ABTS (2,2'-azinobis-[3-ethylthiazoline-6-sulfonic acid])

With regard to ABTS method, the antioxidant activities of various extracts of the two plants varied from 27.94 to 58.42  $\mu\text{mol EAA/g}$  extract (Figure 2). But ethanolic extract of bark of *G. erubescens* showed the best antioxidant activity compared to those of the other extracts (aqueous and ethanolic extracts of leaves of *G. erubescens*, of whole plant of *F. agrestis* and aqueous extract of bark of *G. erubescens*). However, compared to the controls (quercetin and trolox), the ability of ethanolic extract of bark of *G. erubescens* to reduce the cation radical  $\text{ABTS}^{\bullet+}$  was very low. In view of these results, the antioxidant activity of our various extracts by ABTS method was not interesting enough.

### FRAP (Ferric Reducing Antioxidant Power)

Regarding the ability to reduce ferric ions, the antioxidant activities of ethanolic and aqueous extracts of two plants varied from 11.52 to 39.24  $\mu\text{mol EAA/g}$  extract. The aqueous extracts from leaves of *G. erubescens* and whole plant of *F. agrestis* had the best antioxidant activities compared to those of the other extracts. However, the ability of aqueous extracts from leaves of *G. erubescens* and whole plant of *F. agrestis* to reduce iron III to iron II was very low compared to that of trolox but similar to that of quercetin (Figure 3). In view of these results, the aqueous extracts of the leaves of *G. erubescens* and of the whole plant of *F. agrestis* had interesting antioxidant activities by FRAP method.

## 9. Determination of Antiplasmodial Activity *in Vivo*

### Impact of aqueous and ethanolic on number of white bloods cells

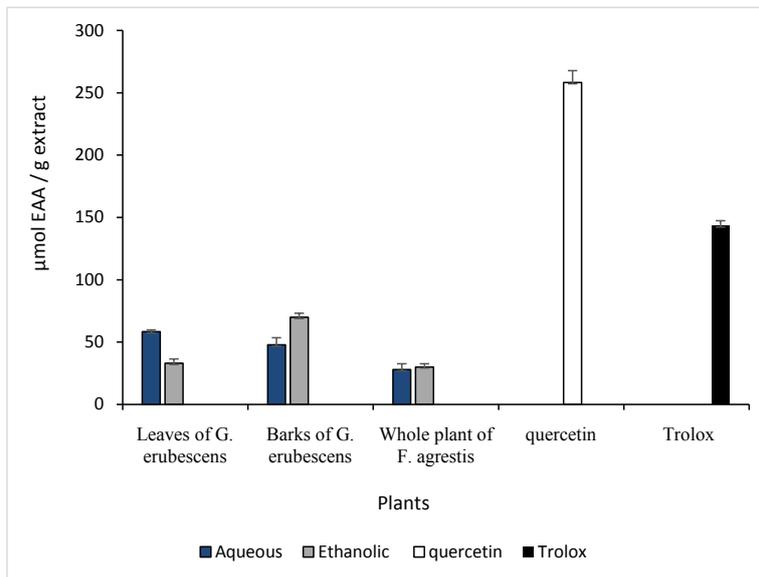
With regard to Figure 4, the number of white blood cells obtained after treatment of malaria with the different extracts of two plants was between 19 and 40. However, there was no significant difference between the number of white blood cells obtained after treatment with ethanolic and aqueous extracts ( $p\text{-value} = 1$ ) of leaves of *G. erubescens*. There was also no significant difference between two extracts ( $p\text{-value} = 0.09$ ) of bark of *G. erubescens*. The same is true for extracts ( $p\text{-value} = 0.99$ ) of whole plant of *F. agrestis*.

The parasitaemia reduction percentages of ethanolic and aqueous extracts of leaves and bark of *G. erubescens*, as well as those of whole plant extracts of *F. agrestis* were between 10% and 50%. According to the scale of [16], these percentages of reduction were moderate (Figure 5).

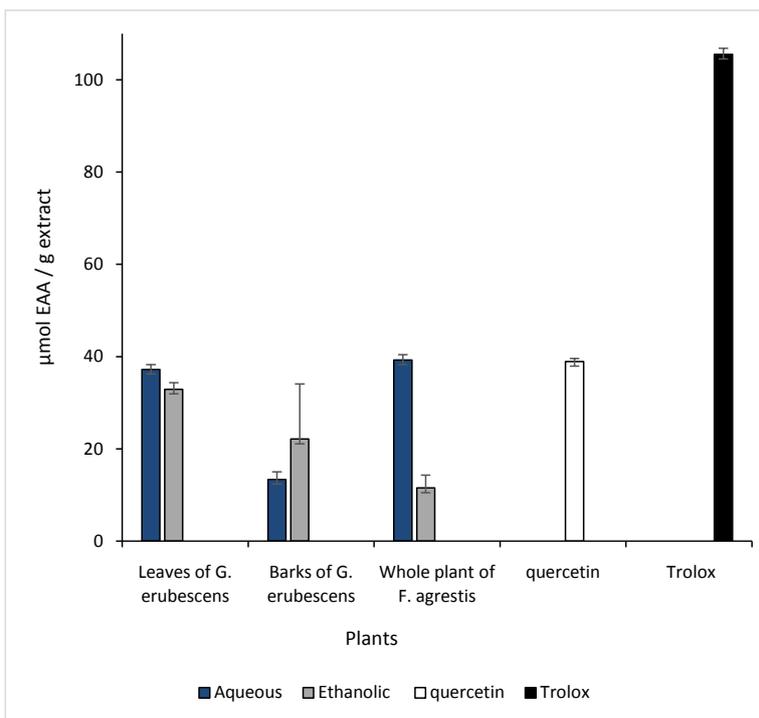
## 10. Discussion

In this study, the secondary metabolites, more precisely the total phenolics and total flavonoids, were determined by the method described in [13]. All the extracts were rich in total phenolics and flavonoids but their contents varied from one extract to another. This variation could be explained by the fact that the total phenolic and flavonoid contents varied according to the season and the geographical location [17] of the different plants. These results could also be explained by the extraction conditions (sample/solvent sample, extraction time,

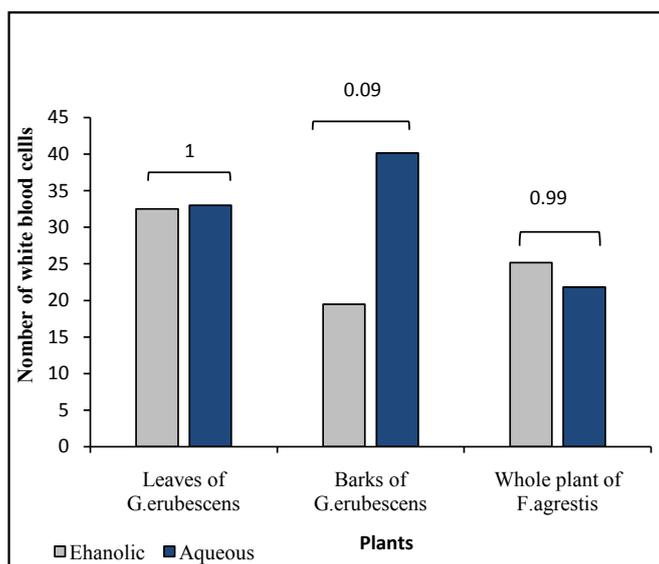
temperature) [18]. As for the antioxidant activity, all the extracts by the three methods namely DPPH, ABTS and FRAP had exhibited antioxidant activities. The presence of these activities within these various extracts could be due to the phenolics and total flavonoids previously measured in this study. As a reminder, total phenolics and total flavonoids are considered to be very powerful natural



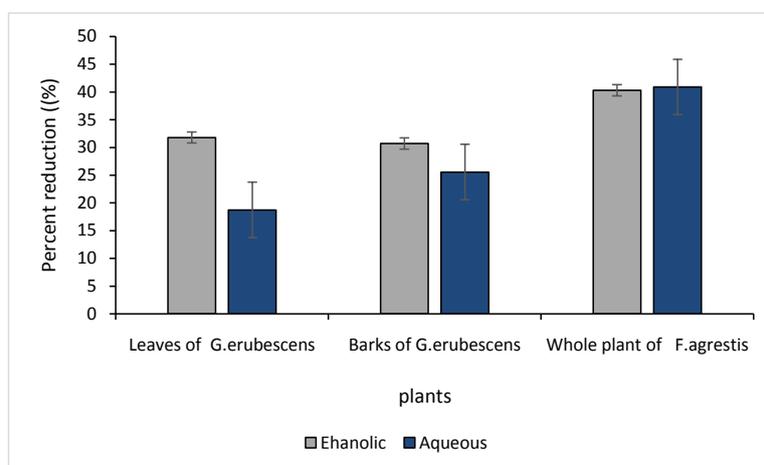
**Figure 2.** Capacity antioxidant of the different extracts with ABTS method from *G. erubescens* and Whole plant of *F. agrestis* (as compared to quercetin and trolox).



**Figure 3.** Antiradical activity of aqueous and ethanolic extracts with FRAP method from *G. erubescens* and Whole plant of *F. agrestis* (as compared to quercetin and trolox).



**Figure 4.** Impact of aqueous and ethanolic extracts of Whole plant of *F. agrestis*, leaves and bark of *G. erubescens* on number of white blood cells (comparison of ethanolic and aqueous extracts from each part of plants), P-value  $\geq 0.005$ .



**Figure 5.** The percentage reduction of ethanolic and aqueous extracts of the leaves and bark of *G. erubescens* and of the whole plant of *F. agrestis*.

antioxidants responsible for the antioxidant activities of plants. These compounds are therefore efficient donors of hydrogen to the ABTS and DPPH radicals, hence their stability, thus giving an antioxidant power to our various extracts [19]. As for the FRAP method, the best antioxidant activities were observed at the level of the aqueous extracts of the leaves of *G. erubescens* and of the whole plant of *F. agrestis* and these extracts also had the best contents of total flavonoids. In addition, these extracts had the same antioxidant activities as quercetin (control). There was a positive link between the antioxidant activity and the content of total flavonoids [20] [21] [22] [23]. Thus, the good antioxidant activity of these two extracts could be due to their high content of total flavonoids. Regarding the number of white blood cells, the different extracts of two

plants had the same impacts on the number of blood cells after treatment for malaria. These results could be explained by inflammatory reactions occurring during the injection of various plant extracts, considered to be foreign bodies for the body. In fact, inflammation is the first reaction to an attack on the body [24]. This inflammation will lead to an increase in the number of white blood cells, particularly neutrophils which are the first cells to arrive in large numbers at the site of inflammation [25]. During malaria there is an increased rate of lipoperoxidation which leads to an increase in parasitaemia [26]. In addition, the electrons produced during the oxidation of Fe II to Fe III following the degradation of hemoglobin by the parasite react with molecular oxygen to form free radicals [27]. These different phenomena lead to a decrease in the antioxidant system and to an increase in parasitaemia. Thus, the total phenolics and flavonoids which represent antioxidants dosed in our extracts could be at the origin of the inhibition of the production of reactive species leading to moderate reduction percentages of the parasitaemia of all the aqueous and ethanolic extracts of the two plants.

## 11. Conclusion

In present work, efficacy of ethanolic and aqueous extracts from leaves and bark of *G. erubescens* and whole plant of *F. agrestis* was investigated. For this, quantification of total phenolic and flavonoid compounds and evaluation of their antioxidant and antiplasmodial activities were carried out. The ethanolic extract of leaves of *G. erubescens* and the aqueous extracts of bark of *G. erubescens* and whole plant of *F. agrestis* have presented the best total phenolics and total flavonoids contents, respectively. The ethanolic extract of the leaves of *G. erubescens* and aqueous extracts of bark of *G. erubescens* and whole plant of *F. agrestis* have demonstrated the best antioxidant activities. The impact of extracts of the two plants on the number of white blood cells count was similar to the control, and parasitaemia reduction percentages were moderate. The results obtain in this study allow to justify the traditional uses of *Gardenia erubescens* and *Fadogia agrestis* to treat of malaria in Burkina Faso.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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