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Antityphoid and antioxidant activities of hydroethanolic leaf extract of *Adenia lobata* Jacq. (Passifloraceae) on *Salmonella typhi* infected wistar rats

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Abstract
Typhoid fevers are a major public health problem, especially in developing countries where they are endemic. In order to contribute to the search for new antityphic substances, medicinal plants are a good source of new antityphic molecules accessible by everyone. In this study, the *in vivo* antisalmonellal activity of the hydroethanolic leaves extract of *Adenia lobata* was evaluated in albino rats infected with *Salmonella Typhi* (ATCC 6539) and the antioxidant activity of this extract was evaluated after treatment. *In vivo* antisalmonellal activity was assessed by the blood culture method on Wistar rats infected by *S. Typhi* (ATCC 6539), and oxidative stress biochemical parameters (superoxide dismutase, catalase, glutathione, malondialdehyde, nitric oxide) were evaluated after treatment. Phytochemical screening was performed to justify these activities.
The hydroethanolic leaves extract of *Adenia lobata* at different doses (5. 45 and 90 mg/kg of body weight) resulted in the healing of infected rats between the eighth and twelfth day of treatment. Extract treatment reduced malondialdehyde levels and increased SOD, catalase, glutathione, and nitric oxide levels in infected rats by normalizing some of this content compared to neutral controls. Phytochemical analysis revealed the presence of flavonoids, alkaloids, steroids, tannins, phenols, saponins, anthocyanins, triterpenes and anthraquinones in the hydroeyhanolic leaves extract of *Adenia lobata*.
These results show that the hydroeyhanolic leaves extract of *Adenia lobata* cures typhoid fever and reduces the state of oxidative stress caused by *S. Typhi* during infection.

Keywords: *Adenia lobata*, Antityphoid, Antioxidant, *Salmonella Typhi*.

1. Introduction
Typhoid and paratyphoid fevers are digestive systemic bacterial infections caused by Salmonella bacteria, respectively *Typhi* and *Paratyphi* (A and B). The World Health Organization (WHO) estimates that 22 million typhoid cases and 216.500 typhoid related deaths occur each year worldwide (WHO, 2014). Although typhoid is essentially considered as an endemic disease, epidemics occur frequently as a result of failures of water supply or sanitation systems. It remains a major public health problem in the continents like Asia, Africa and Latin America (WHO, 2014). In Cameroon, typhoid fever is endemic with outbreaks limited in time and space. The most recent data shows that 262.149 in December 2016 (compared to 241.935 at the end of November 2016) cases were notified at the national level against 220.337 cases in 2015 (OMS, 2016) [21].
The existing means of control are antibiotics, of which the most used are fluoroquinolones and third generation cephalosporins (Boulo *et al.*, 2011) [7]. However, the situation is all the more worrying, since in recent years, *Salmonella Typhi* and *Paratyphi* have been developing resistance to antibiotics present in the market (Cooke and Wain, 2004) [9].
In many developing countries, access to conventional medicine remains limited to large cities. Travel difficulties, lack of qualified personnel, high cost of conventional medicines and benefits, and socio-economic conditions (precariousness of hygiene, illiteracy and limited access to health care and vaccines), leave much of the population no choice but traditional medicine to treat common diseases (Sanogo, 2006) [25]. Alternative medicine is commonly used to treat or prevent chronic, common diseases and to improve the quality of life. In Africa,

more than 80% of the population use traditional medicine and medicinal plants for their primary health care (Sanogo, 2006) [25]. The manifestations of typhoid fever are sometimes severe and can lead to death in 30% of cases of complications in the absence of adequate treatment (Bhutta *et al.*, 2006) [6]. Moreover, during salmonella infection, or following exposure of the body to exogenous toxins, the production of free radicals such as superoxide anion and nitric oxide (O., NO.), although controlled by antioxidant defense systems under normal physiological conditions, can increase and engender oxidative stress (Vazquez-Torres *et al.*, 2000) [30]. This state of stress is implicated in most human diseases as a triggering factor or associated with complications (Favier, 2003) [13]. That is why it is important to look for new drugs that can address this public health problem. Medicinal plants and knowledge about medicinal plants are an important heritage of the African continent (Sanogo, 2006) [25]. *Adenia lobata* belongs to these medicinal plants because it is used in traditional medicine to fight against rheumatic pains and abdominal pains. *Adenia lobata* is also used to treat coughs, bronchitis and fever. Some studies have shown that *Adenia lobata* has antihyperglycemic activities (Sarkodie *et al.*, 2013) [26], antioxidants (konan *et al.*, 2011; Agoreyo *et al.*, 2012) [18, 2]. The objective of this work was to evaluate the *in vivo* antisalmonellal and antioxidant activities of the hydroethanolic extract of *A. lobata* on *Salmonella Typhi* ATCC6539.

2. Methods

2.1 Plant material

The leaves of *Adenia lobata* were harvested in Bandjoun in the Koung-Khi division (western region of Cameroon) in September 2016. The identification was made at the National Herbarium of Cameroon (Yaoundé by Botanist Dr. TCHIENGUE Barthélemy) in comparison with the reference sample kept under number 43292/HNC.

2.2 Preparation of plant extract

The leaves of *Adenia lobata* were harvested, dried out of the sun (about 25°C) and crushed. The powder obtained was used to prepare the hydroethanol extract (70% ethanol). This preparation was made for 48 hours, by maceration of 100 g of powder in one liter (1 L) of 70% ethanol with stirring twice a day. The mixture (solvent and extract) obtained was filtered with Whatman paper N°1. The filtrate was subsequently left in an oven set at 45 °C for two days for complete evaporation of hydroethanol solvents.

2.3 Bacteria and culture medium

The microorganism used in this work consisted of a strain of *Salmonella Typhi* collection "American Type Culture Collection" (ATCC 6539) from the Laboratory of Bacteriology, Pasteur Center, Yaounde (Cameroon) and *Salmonella-Shigella* agar (Italy Liofilchem) was used for the activation of the bacterial strain, and for the evaluation of *Salmonella* burden in the blood of rats during the *in vivo* antisalmonellal study.

2.4 Aminal treatment

Forty-eight male and female albino rats aged 08 to 10 weeks were divided into 12 groups of 4 animals each, including 6 groups of males and 6 groups of females. The selected animals were acclimated for one week. With the exception of group 6 animals (uninfected and untreated), which was the neutral control, all other groups (1-5) were infected. They received orally, a single dose (1 mL) of 1.5×10^8 CFU suspension of *Salmonella Typhi* (ATCC 6539). Infection monitoring in animals was done by colony-counting blood culture on *Salmonella-Shigella* agar and converted to CFU *salmonella* per milliliter of blood. The effectiveness of the infection was deduced when the blood culture of the animals had a concentration $\geq 4 \times 10^5$ CFU ml of blood, which was marked by the excretion of liquid stools, the presence of mucus in the stool, the reduced activity and exponential increase in systemic load in *S. Typhi* in rats. After infection, animals in group 5 (Infected and untreated) who were the negative control, received no treatment while animals in group 4 (positive control) were treated with ciprofloxacin (14 mg/kg of body weight). Animals from group 1 to 3 received after infection, treatment at different doses of plant extract (5. 45 and 90 mg/kg of body weight respectively). These doses were obtained on the basis of the traditional practitioner's dose (90 mg/kg of body weight). During the test, the animals were well fed and the food intake was made as a function of time.

2.5 Preparation of serum and various organ homogenates

The day following the end of the treatment, the animals were subjected to a 12hr diet, then weighed and anesthetized with chloroform vapor. The anesthetized animals were placed in a supine position on a board with a wide open abdomen. A dissection was performed from the lower part to the abdomen. The blood was collected by cardiac puncture and then introduced into tubes. Left standing in an ice bath for 6 hours, these tubes were centrifuged at 3000 rpm for 15 minutes; which made it possible to obtain the serum. The homogenates of the various organs (heart, kidneys, liver, lung and spleen) were prepared at 15% in phosphate buffer (pH 7.2. 0.2M).

2.6 Determination of the relative weight of organs

The relative weight of the organs of each rat was determined by the following formula:

Relative weight (%) = (Organ weight/Body weight) × 100

2.7 Evaluation of parameters related to oxidative stress

The sera and homogenates thus obtained were aliquoted and stored at -4°C, for the assays of the parameters related to oxidative stress (SOD, catalase, glutathione, malondialdehyde, nitric oxide).

2.7.1 Determination of superoxide dismutase (SOD)

Principle: The presence of superoxide dismutase (SOD) in a sample inhibits the oxidation of adrenaline to adrenochrome. The increase in absorbance read at 480 nm is proportional to the activity of superoxide dismutase.

Procedure: It was determined by the method of Misra and Fridovich (1972) with some modifications. To do this, to 150 µl of homogenates were added 500 µl of carbonate-bicarbonate buffer (pH 10.2. 0.3M, pKa 10.3), then 250 µl of an EDTA solution (0.6 mM), and 350 µl distilled water. The mixture obtained was homogenized and 250 µl of adrenaline (4.5 µm) was added in order to initiate the reaction. Autooxidation of adrenaline was measured by reading the OD at 480 nm 30 seconds and 180 seconds after adding epinephrine.

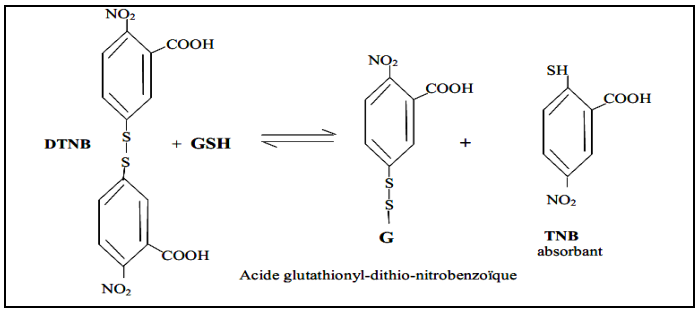
SOD activity expressed as percentage inhibition was calculated as follows:

% inhibition = [100- (ΔOD sample/ΔOD blank)] x 100

Knowing that 50% inhibition corresponds to one unit of activity.

2.7.2 Determination of glutathione

Principle: The principle is based on the oxidation reaction of GSH with 2.2-dithio-5.5'dinitrobenzoic acid (DTNB) thus releasing thionitrobenzoic acid (TNB) which absorbs at 412 nm. The equation of this reaction is as follows:



Procedure: It was carried out according to Ellman's colorimetric method (Tozan *et al.*, 2006) [28]. To do this, 200 µl of sample was added to 800 µl of $Na_2HPO4.\ 2H_2O$, and then the mixture obtained was homogenized. The optical density was read immediately at 412 nm after addition of the dithiobis-nitrobenzoate prepared in 1% sodium citrate. The glutathione level was calculated using the extinction coefficient of 1.36×10^4 $M^{-1}.cm^{-1}$ and the results were expressed in µmol glutathione/g of tissue.

2.7.3 Determination of catalase

Principle: When the dichromate is brought into contact with acetic acid, it is reduced to chromic acetate which can be measured colorimetrically. The intensity of chromic acid staining is proportional to the amount of non-decomposed H_2O_2 by the catalase present in the tissue homogenates and therefore reflects the inverse of the activity of the latter.

Procedure: It was determined by the method of Dimo *et al.* (2006). To do this, 375 µl of phosphate buffer pH 7.4 was added to 25 µl of tissue homogenate, then 100 µl of H_2O_2 (50 mM). One minute later, 1 ml of potassium dichromate (5%) prepared in 1% acetic acid was introduced into the reaction medium. The mixture obtained was incubated for 10 minutes in a boiling water bath and then cooled in an ice bath. The reading of the optical densities was made at 570 nm against the blank (the extract was replaced by distilled water in the blank tubes). The enzymatic activity of catalase was deduced by the Beer-Lambert law.

2.7.4 Determination of malondialdehyde (MDA)

Principle: Lipid peroxidation was evaluated by the determination of malondialdehyde (MDA) according to the method by Oyedemi *et al.* (2010) [22] with certain modifications. MDA is one of the final products of the decomposition of polyunsaturated fatty acids (PUFAs) under the effect of free radicals released during stress. In acidic and hot medium (pH 2 to 3. 100 °C), an MDA molecule condenses with two thiobarbituric molecules (TBA) to form a pink colored complex (reading at 532 nm).

Procedure: Five hundred microliters of 1% orthophosphoric acid and 500 µl of precipitation mixture (1% thiobarbituric acid in 1% acetic acid) were added to 100 µl of homogenate. The resulting reaction mixture was homogenized and incubated for 15 minutes in a boiling water bath. After quenching in an ice bath, the mixture was centrifuged at 3500 rpm for 10 min. The absorbance of the supernatants was read at 532 nm against the blank. Lipid peroxidation was calculated on the basis of the molaldehyde (MDA) molar extinction coefficient and expressed in micromoles of MDA per gram of tissue using the Beer-Lambert formula.

2.7.5 Determination of nitric oxide (NO)

Principle: NO content in serum and tissue homogenates is measured by Griess reagent. Absorption of the chromophore during ionization of nitrite with sulfanilamide coupled with naphthylethylenediamine (NED) is read at 520 nm (Napolitano *et al.*, 2005) [20].

Procedure: 340 µl of 1% sulfanilamide (prepared in 5% orthophosphoric acid) was introduced into 340 µl of serum and homogenates. The resulting mixture was homogenized and left in the dark for 5 minutes at room temperature. Next, 340 µl of naphthylethylenediamine (0.1% NED) was added to the reaction medium and the whole was left once more in the dark for 5 minutes. The optical densities were read at 520 nm against the blank.

The NO content was determined from a calibration curve derived from the different Na_2NO concentrations.

2.8 Statistical analyzes

The results of the various tests were subjected to analysis of the variance (ANOVA) and expressed in the form of means ± ESM. Differences between means where they existed were assessed using the Waller-Duncan test at the 5% probability level. The SPSS software version 21 for Windows has been used for this purpose.

3. Results

3.1 Phytochemical composition of the hydroethanolic leaves extract of *Adenia lobata*

Table 1 shows the bioactive compounds of the hydroethanolic leaves extract of *A. lobata*. In general, the hydroethanolic extract exhibited all active compounds tested, such as flavonoids, alkaloids, steroids, tannins, phenols, saponins, anthocyanins, triterpenes and anthraquinones.

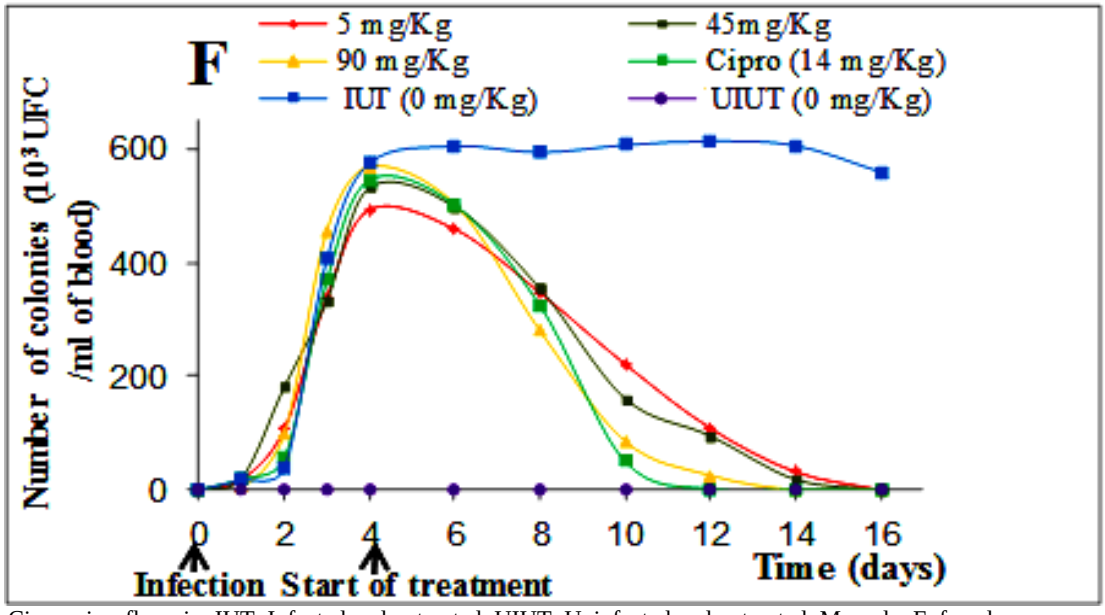
Table 1: Phytochemical composition of the hydroethanolic extract from the leaves of *A. lobata*

Group of metabolites	Leaf extract of *Adenia lobata* (Ethanol 70%)
Flavonoids	+
Alkaloids	+
Steroids	+
Tannins	+
Phenols	+
Saponins	+
Anthocyanin	+
Triterpenes	+
Anthraquinone	+

+: Present; –: Absent.

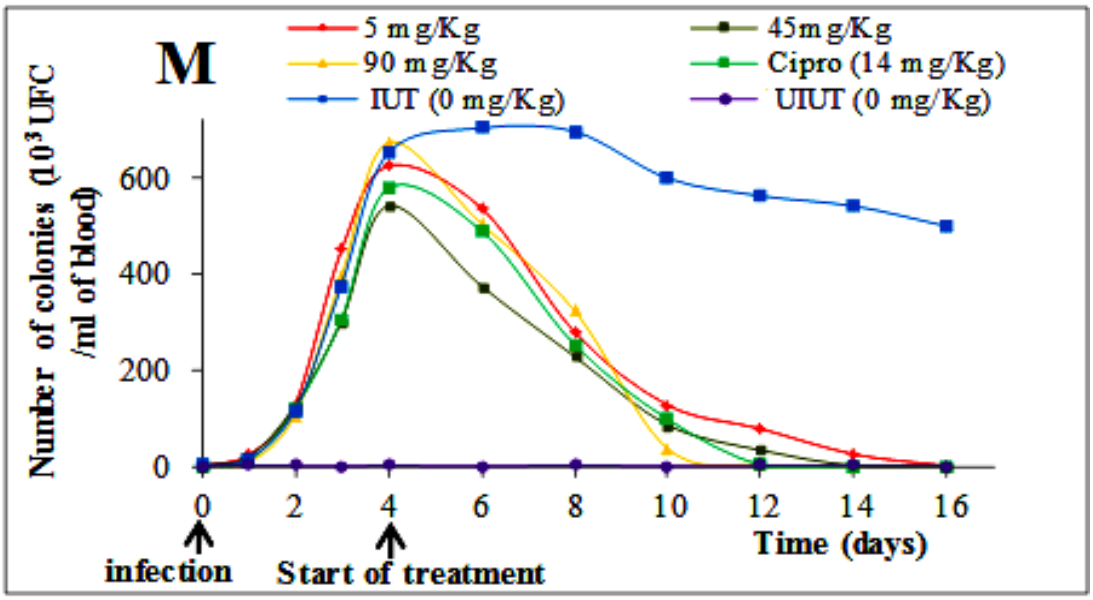
3.2 Antibacterial activity

Figures 1 and 2 show the evolution of the number of *S. Typhi* colonies in the blood of female and male rats respectively. With the exception of the uninfected and untreated animal (UIUT) curves where the bacterial load remained constant as well as infected and untreated animals (IUT), all other curves showed three major phases. The latent phase of a day after infection, during which the number of colonies did not significantly change. Then the exponential phase lasting three days following the infection, which marks a significant (p<0.05) increase in the number of *Salmonella Typhi* colonies (ATCC 6539) in the blood of the animals. Ending with the decline phase lasting 8 to 12 days after infection, marked a significant decrease (p<0.05) in the number of colonies in treated animals by administration of the doses of extracts and ciprofloxacin (positive control). Healing was dose-dependent in males because animals at 90 mg/kg were fully cured on the eighth day of treatment compared to the reference antibiotic (14 mg/kg), while those in the dose 45 mg/kg were cured on the tenth day and those of the dose 5 mg/kg on the twelfth day of treatment. In females however, animals at the 90 mg/kg dose were completely cured at one-tenth and those at the 5 and 45 mg/kg doses were cured on the twelfth day. During the experiment, the number of colonies of infected and untreated animals (negative control) remained significantly (p<0.05) high compared to uninfected and untreated animals (neutral control).



Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated; M: male; F: female.

Fig 1: Effects of *Adenia lobata* extract on the number of *Salmonella Typhi* colonies (ATCC6539) as a function of the time in female rats.

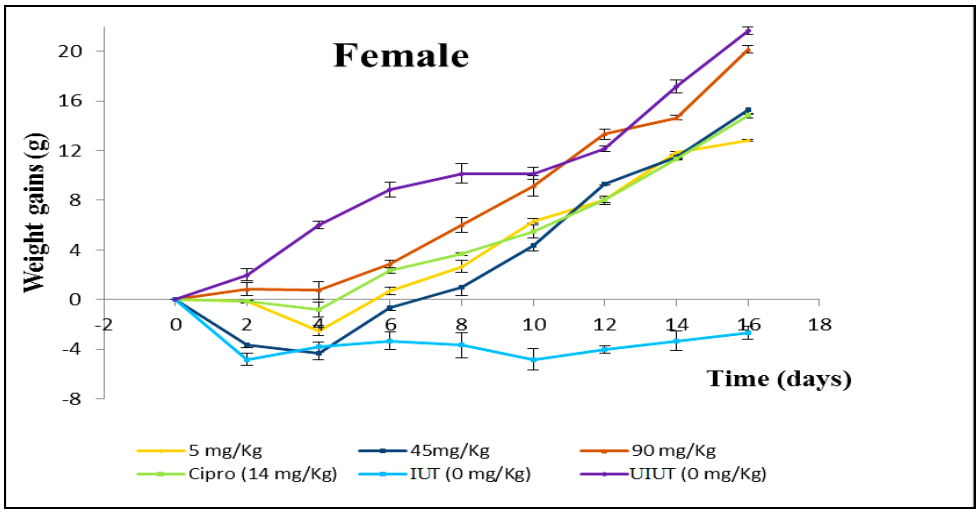


Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated; M: male; F: female.

Fig 2: Effects of *Adenia lobata* extract on the number of *Salmonella Typhi* colonies (ATCC6539) as a function of the time in male rats.

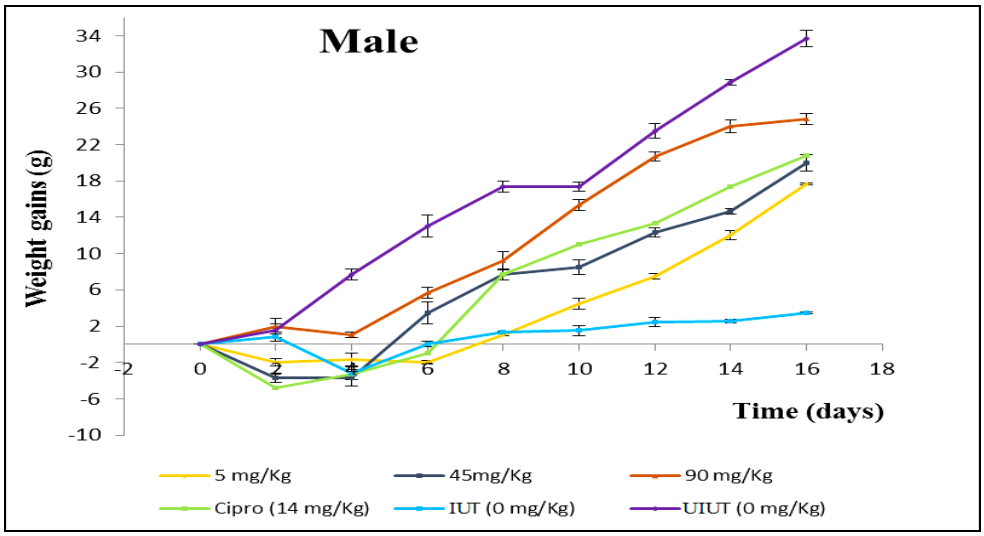
3.3 Food consumption

The evolution of food consumption in rats (females and males) infected and treated with different doses of *Adenia lobata* extract is presented in Figures 3 and 4. In general, the phase of infection induced a significant (p<0.05) decrease in food consumption in all infected animals compared to uninfected and untreated animals (neutral controls). After infection, the treatment phase caused dose-dependent, increased feed intake in both sexes (females and males) compared to infected and untreated animals (IUT).



Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated.

Fig 3: Evolution of food consumption as a function of time in females infected with *Salmonella Typhi* and treated with different doses of *Adenia lobata* extract.



Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated

Fig 4: Evolution of food consumption as a function of time in males infected with *Salmonella Typhi* and treated with different doses of *Adenia lobata* extract.

3.4 Relative weight of organs

Table 2 shows the effect of treatment on the relative weight of the organs of female and male rats. In a general way, the relative weight of the organs of the treated rats (two sexes) at different doses of extract was insignificant ($p \geq 0.05$) compared with controls (UIUT and IUT). However, the infection resulted in a significant ($p<0.05$) increase in relative heart weight in female rats compared to neutral controls.

Table 2: Effects of different doses of leaf extract *Adenia lobata* on the relative weight of rat organs.

Sex and Doses	Organs and relative weight (g/100 g of body weight)				
	Heart	Liver	Kidneys	Spleen	Lungs
Female					
5 mg/Kg	0.37 ± 0.01^{b}	3.65 ± 0.09^{a}	0.70 ± 0.03^{a}	0.35 ± 0.15^{a}	0.60 ± 0.07^{a}
45mg/Kg	0.33 ± 0.01^{a}	3.60 ± 0.21^{a}	0.66 ± 0.07^{a}	0.30 ± 0.07^{a}	0.56 ± 0.04^{a}
90 mg/Kg	0.32 ± 0.02^{a}	3.40 ± 0.15^{a}	0.63 ± 0.05^{a}	0.26 ± 0.04^{a}	0.58 ± 0.02^{a}
Cipro (14 mg/Kg)	0.38 ± 0.02^{b}	3.65 ± 0.04^{a}	0.68 ± 0.04^{a}	0.40 ± 0.12^{a}	0.61 ± 0.07^{a}
IUT (0 mg/Kg)	0.43 ± 0.01^{c}	3.73 ± 0.09^{a}	0.76 ± 0.07^{a}	0.41 ± 0.05^{a}	0.77 ± 0.20^{a}
UIUT (0 mg/Kg)	0.34 ± 0.02^{a}	3.67 ± 0.15^{a}	0.67 ± 0.11^{a}	0.35 ± 0.08^{a}	0.52 ± 0.05^{a}
Male					
5 mg/Kg	0.31 ± 0.01^{a}	3.34 ± 0.24^{a}	0.57 ± 0.13^{a}	0.39 ± 0.06^{a}	0.56 ± 0.06^{a}
45mg/Kg	0.29 ± 0.04^{a}	3.28 ± 0.15^{a}	0.66 ± 0.01^{a}	0.43 ± 0.13^{a}	0.60 ± 0.03^{a}
90 mg/Kg	0.30 ± 0.06^{a}	3.23 ± 0.15^{a}	0.64 ± 0.04^{a}	0.31 ± 0.09^{a}	0.58 ± 0.07^{a}
Cipro (14 mg/Kg)	0.35 ± 0.04^{a}	3.43 ± 0.16^{a}	0.66 ± 0.01^{a}	0.38 ± 0.04^{a}	0.61 ± 0.07^{a}
IUT (0 mg/Kg)	0.39 ± 0.06^{a}	3.78 ± 0.39^{a}	0.69 ± 0.10^{a}	0.48 ± 0.08^{a}	0.68 ± 0.05^{a}
UIUT (0 mg/Kg)	0.33 ± 0.06^{a}	3.48 ± 0.60^{a}	0.65 ± 0.09^{a}	0.38 ± 0.13^{a}	0.59 ± 0.07^{a}

The table values are presented as mean ± ESM of 4 repetitions. In the same column and for the same sex, the values bearing the different letters are significantly different ($p<0.05$). Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated.

3.4 Effects of treatment on biochemical markers related to oxidative stress

3.4.1 Effects of treatment of different doses of extract on the activity of superoxide dismutase (SOD)

Table 3 presents the activities of SOD in the different tissues and sera of male and female rats. It appears that the infection resulted in a significant ($p<0.05$) reduction in SOD activity in all organs and sera of female and male animals compared to neutral controls (UIUT). In addition, this activity remained insignificant ($p\geq 0.05$) in the liver and kidneys of male rats compared to the same control.

In general, treatment significantly ($p<0.05$) increased SOD activity in all the tested animal organs and sera compared to negative controls (IUT). This increase, although it existed, was insignificant ($p\geq 0.05$) in the liver and kidneys of male rats compared to this same control.

However, treatment normalized ($p\geq 0.05$) SOD activity in all organs and serum of female rats and in the hearts of male rats treated at different doses of extract compared to neutral control.

Table 3: Effects of treatment on the activity of superoxide dismutase (SOD) in sera and tissues of rats.

Sex and Doses	Organs and Quantity of SOD (activity/mg of tissues et activity/ml of blood)					
	Serum	Heart	Liver	Kidneys	Spleen	Lungs
Female						
5 mg/Kg	0.18 ± 0.01^{b}	2.04 ± 0.14^{b}	0.47 ± 0.04^{b}	2.20 ± 0.18^{b}	1.92 ± 0.41^{b}	2.08 ± 0.43^{b}
45mg/Kg	0.20 ± 0.01^{b}	4.24 ± 1.45^{c}	0.49 ± 0.02^{b}	2.45 ± 0.53^{b}	2.44 ± 0.23^{b}	1.98 ± 0.26^{b}
90 mg/Kg	0.21 ± 0.02^{b}	4.12 ± 0.42^{c}	0.53 ± 0.02^{b}	2.57 ± 0.05^{b}	2.40 ± 0.16^{b}	2.33 ± 0.35^{b}
Cipro (14 mg/Kg)	0.21 ± 0.01^{b}	3.39 ± 0.36^{c}	0.47 ± 0.03^{b}	2.43 ± 0.23^{b}	1.91 ± 0.34^{b}	2.14 ± 0.17^{b}
IUT (0 mg/Kg)	0.14 ± 0.01^{a}	1.80 ± 0.07^{a}	0.40 ± 0.01^{a}	1.76 ± 0.09^{a}	1.34 ± 0.06^{a}	0.74 ± 0.19^{a}
UIUT (0 mg/Kg)	0.19 ± 0.03^{b}	3.65 ± 0.15^{c}	0.48 ± 0.03^{b}	2.31 ± 0.29^{b}	2.55 ± 0.41^{b}	1.97 ± 0.31^{b}
Male						
5 mg/Kg	0.14 ± 0.01^{b}	2.95 ± 0.14^{b}	0.54 ± 0.08^{ab}	2.97 ± 0.47^{a}	1.75 ± 0.06^{b}	1.08 ± 0.04^{b}
45mg/Kg	0.16 ± 0.00^{b}	3.33 ± 0.65^{b}	0.48 ± 0.04^{a}	2.38 ± 0.24^{a}	1.67 ± 0.04^{b}	1.09 ± 0.12^{b}
90 mg/Kg	0.15 ± 0.01^{b}	3.18 ± 0.22^{b}	0.52 ± 0.03^{ab}	2.47 ± 0.69^{a}	2.49 ± 0.26^{c}	1.27 ± 0.08^{b}
Cipro (14 mg/Kg)	0.17 ± 0.01^{c}	2.76 ± 0.22^{b}	0.58 ± 0.01^{b}	2.68 ± 0.24^{a}	2.35 ± 0.33^{c}	1.46 ± 0.40^{bc}
IUT (0 mg/Kg)	0.10 ± 0.02^{a}	2.00 ± 0.16^{a}	0.43 ± 0.02^{a}	2.17 ± 0.36^{a}	1.11 ± 0.37^{a}	0.73 ± 0.17^{a}
UIUT (0 mg/Kg)	0.19 ± 0.01^{c}	3.22 ± 0.48^{b}	0.46 ± 0.04^{ab}	2.51 ± 0.35^{a}	2.44 ± 0.22^{c}	1.99 ± 0.17^{c}

The table values are presented as mean ± ESM of 4 repetitions. In the same column and for the same sex, the values bearing the different letters are significantly different ($p<0.05$). Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated.

3.4.2 Effects of treatment of different doses of extract on catalase activity

The effect of treatment of the extract doses on catalase activity in the tissues and sera of male and female rats is shown in Table 4.

It appears that the infection resulted in a significant ($p<0.05$) reduction in catalase activity in all organs and sera of female and male animals compared to neutral controls (UIUT).

The treatment resulted in a significant ($p<0.05$) increase in catalase activity in almost all organs and sera of the tested rats compared to the negative controls (IUT). Furthermore, this activity was insignificant ($p\geq 0.05$) at the 5 mg/kg dose in the liver and kidneys of male rats and in the kidneys of female rats compared to the same controls.

However, treatment regulated ($p\geq 0.05$) catalase activity in the serum, liver, spleen and lung of female and male rats treated at different doses of extract compared to neutral control. Although there was an increase, catalase activity was significant ($p<0.05$) at the 5 mg/Kg dose in the heart and kidneys of male rats and, in the kidneys of female rats compared to the same witnesses.

Table 4: Effects of treatment on catalase activity in rat blood and tissues.

Sex and Doses	Organs and Quantity of catalase (µmol/min/mg of tissues and µmol/min/ml of blood)					
	Serum	Heart	Liver	Kidneys	Spleen	Lungs
Female						
5 mg/Kg	0.50 ± 0.07^{b}	2.96 ± 0.72^{b}	5.09 ± 1.02^{b}	2.68 ± 0.29^{a}	8.59 ± 1.65^{b}	4.35 ± 0.38^{b}
45mg/Kg	0.50 ± 0.04^{b}	3.27 ± 0.23^{b}	6.12 ± 1.93^{b}	4.37 ± 0.16^{c}	6.96 ± 0.16^{b}	4.42 ± 0.59^{b}
90 mg/Kg	0.51 ± 0.07^{b}	2.86 ± 0.47^{b}	6.40 ± 1.28^{b}	3.73 ± 0.40^{bc}	7.33 ± 1.11^{b}	5.80 ± 1.96^{b}
Cipro (14 mg/Kg)	0.54 ± 0.07^{b}	3.81 ± 0.51^{b}	6.35 ± 0.63^{b}	3.22 ± 0.18^{b}	8.61 ± 0.62^{ab}	4.87 ± 0.98^{b}
IUT (0 mg/Kg)	0.40 ± 0.01^{a}	1.71 ± 0.22^{a}	3.61 ± 0.20^{a}	2.27 ± 0.15^{a}	5.15 ± 0.11^{a}	2.69 ± 0.08^{a}
UIUT (0 mg/Kg)	0.55 ± 0.07^{b}	5.08 ± 0.79^{c}	6.53 ± 0.36^{b}	4.14 ± 0.10^{c}	10.26 ± 0.72^{b}	4.06 ± 0.78^{b}
Male						
5 mg/Kg	0.40 ± 0.02^{b}	1.51 ± 0.25^{a}	5.52 ± 0.66^{b}	3.13 ± 0.22^{a}	8.34 ± 0.43^{b}	3.97 ± 0.65^{b}
45mg/Kg	0.42 ± 0.04^{b}	4.00 ± 1.89^{b}	5.07 ± 0.75^{b}	4.77 ± 1.02^{b}	7.98 ± 1.08^{b}	3.99 ± 0.70^{b}
90 mg/Kg	0.42 ± 0.06^{b}	3.18 ± 0.72^{b}	6.30 ± 0.02^{bc}	4.80 ± 0.30^{b}	7.10 ± 0.09^{b}	3.97 ± 0.99^{b}
Cipro (14 mg/Kg)	0.44 ± 0.02^{b}	2.93 ± 0.56^{b}	7.36 ± 1.17^{c}	4.94 ± 0.21^{b}	6.53 ± 0.49^{b}	3.80 ± 0.79^{b}
IUT (0 mg/Kg)	0.29 ± 0.01^{a}	1.37 ± 0.20^{a}	3.06 ± 0.59^{a}	2.87 ± 0.60^{a}	4.59 ± 0.71^{a}	2.64 ± 0.06^{a}
UIUT (0 mg/Kg)	0.46 ± 0.03^{b}	3.22 ± 0.20^{b}	5.46 ± 1.24^{b}	4.98 ± 1.07^{b}	7.57 ± 0.60^{b}	3.32 ± 0.18^{b}

The table values are presented as mean ± ESM of 4 repetitions. In the same column and for the same sex, the values bearing the different letters are significantly different ($p<0.05$). Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated.

3.4.3 Effects of treatment of different doses of extract on glutathione (GSH)

Table 5 shows the effect of treatment on glutathione levels in the tissues and sera of male and female rats.

It appears that the infection resulted in a significant ($p<0.05$) reduction in glutathione levels in the serum, liver and spleen of female and male rats, as well as in the hearts of male rats compared to neutral controls (UIUT). Furthermore, this rate

was insignificant ($p \geq 0.05$) in the heart, kidneys and lungs of female rats as well as in the kidneys and lungs of male rats compared to neutral controls.

Treatment resulted in a significant ($p<0.05$) increase in glutathione levels in the serum, liver and spleen of the tested rats, as well as in the hearts of male rats compared to negative controls (IUT). Moreover, this rate was insignificant ($p \geq 0.05$) in the heart, kidneys and lungs of female rats as well as in the kidneys and lungs of male rats compared to the same controls. However, the treatment normalized ($p \geq 0.05$) at all doses, the glutathione level in the serum, liver, spleen of female and male rats as well as in the heart of male rats at a dose of 5 mg/kg compared to the neutral witness. In addition, a significant ($p<0.05$) increase in glutathione levels was observed in the hearts of male rats at doses of 5 and 45 mg/kg compared to the same controls.

Table 5: Effects of the treatment on glutathione activity in the blood and tissues of rats.

Sex and Doses	Organs and Quantity of Glutathion (µmole/g of tissues and µmole/ml of blood)					
	Serum	Heart	Liver	Kidneys	Spleen	Lungs
Female						
5 mg/Kg	0.11 ± 0.01^{b}	0.57 ± 0.08^{a}	1.03 ± 0.15^{b}	0.48 ± 0.06^{a}	0.84 ± 0.04^{b}	0.68 ± 0.04^{a}
45mg/Kg	0.13 ± 0.01^{bc}	0.55 ± 0.11^{a}	0.92 ± 0.10^{b}	0.46 ± 0.03^{a}	0.72 ± 0.13^{b}	0.71 ± 0.01^{a}
90 mg/Kg	0.14 ± 0.03^{bc}	0.66 ± 0.15^{a}	1.00 ± 0.03^{b}	0.49 ± 0.01^{a}	0.75 ± 0.10^{b}	0.66 ± 0.05^{a}
Cipro (14 mg/Kg)	0.16 ± 0.00^{c}	0.58 ± 0.11^{a}	1.03 ± 0.03^{b}	0.49 ± 0.01^{a}	0.80 ± 0.05^{b}	0.66 ± 0.06^{a}
IUT (0 mg/Kg)	0.05 ± 0.01^{a}	0.45 ± 0.06^{a}	0.74 ± 0.04^{a}	0.41 ± 0.09^{a}	0.48 ± 0.03^{a}	0.64 ± 0.06^{a}
UIUT (0 mg/Kg)	0.11 ± 0.01^{b}	0.56 ± 0.05^{a}	1.04 ± 0.07^{b}	0.50 ± 0.06^{a}	0.79 ± 0.01^{b}	0.65 ± 0.04^{a}
Male						
5 mg/Kg	0.08 ± 0.01^{b}	0.58 ± 0.03^{b}	1.05 ± 0.08^{b}	0.47 ± 0.09^{a}	0.85 ± 0.02^{c}	0.62 ± 0.08^{a}
45mg/Kg	0.09 ± 0.01^{b}	0.76 ± 0.04^{c}	0.90 ± 0.20^{b}	0.54 ± 0.03^{a}	0.75 ± 0.06^{b}	0.71 ± 0.03^{a}
90 mg/Kg	0.09 ± 0.02^{b}	0.79 ± 0.05^{c}	0.99 ± 0.11^{b}	0.56 ± 0.03^{a}	0.85 ± 0.04^{bc}	0.71 ± 0.03^{a}
Cipro (14 mg/Kg)	0.08 ± 0.01^{b}	0.63 ± 0.03^{b}	1.07 ± 0.09^{b}	0.51 ± 0.04^{a}	0.78 ± 0.07^{bc}	0.62 ± 0.07^{a}
IUT (0 mg/Kg)	0.05 ± 0.01^{a}	0.52 ± 0.01^{a}	0.60 ± 0.02^{a}	0.50 ± 0.08^{a}	0.50 ± 0.02^{a}	0.58 ± 0.10^{a}
UIUT (0 mg/Kg)	0.13 ± 0.05^{b}	0.67 ± 0.02^{b}	0.93 ± 0.06^{b}	0.53 ± 0.01^{a}	$0.83 \pm 0.04b^{c}$	0.62 ± 0.02^{a}

The table values are presented as mean ± ESM of 4 repetitions. In the same column and for the same sex, the values bearing the different letters are significantly different ($p<0.05$). Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated.

3.4.4 Effects of treatment of different doses of extract on malondialdehyde (MDA)

Table 6 shows the change in malondialdehyde levels in the tissues and sera of male and female rats treated.

In general, the infection resulted in a significant ($p<0.05$) increase in malondialdehyde levels in all organs and serum of female and male rats compared to neutral controls (UIUT).

At all doses, treatment resulted in a significant ($p<0.05$) decrease in MDA levels in almost all organs and serum of rats compared to negative controls (IUT). In addition, the MDA level was insignificant ($p \geq 0.05$) only in the hearts of male rats at a dose of 5 mg/kg compared with the same controls.

However, treatment standardized ($p \geq 0.05$) at all doses the MDA level in all organs and serum of female rats and in the serum, heart, liver of male rats compared to neutral controls.

Table 6: Effects of the treatment on malondialdehyde (MDA) level in the blood and tissues of rats.

Sex and Doses	Organs and Quantity of Malondialdehyde (µM/g of tissues and µM/ml of blood)					
	Serum	Heart	Liver	Kidneys	Spleen	Lungs
Female						
5 mg/Kg	1.15 ± 0.27^{a}	3.00 ± 1.26^{a}	0.59 ± 0.18^{ab}	2.17 ± 0.38^{ab}	14.75 ± 0.31^{b}	2.86 ± 0.80^{b}
45mg/Kg	1.24 ± 0.27^{a}	3.97 ± 1.60^{a}	0.78 ± 0.15^{b}	2.68 ± 0.46^{b}	6.27 ± 0.91^{a}	3.27 ± 0.57^{b}
90 mg/Kg	1.00 ± 0.15^{a}	4.29 ± 0.62^{a}	0.69 ± 0.18^{ab}	2.88 ± 0.26^{b}	7.47 ± 1.95^{a}	2.69 ± 0.56^{b}
Cipro (14 mg/Kg)	1.50 ± 0.40^{a}	3.48 ± 1.09^{a}	0.37 ± 0.17^{a}	1.69 ± 0.11^{a}	7.06 ± 0.53^{a}	1.53 ± 0.26^{a}
IUT (0 mg/Kg)	2.55 ± 0.48^{b}	7.36 ± 0.83^{b}	1.75 ± 0.21^{c}	5.34 ± 0.41^{c}	17.58 ± 1.88^{c}	5.51 ± 1.04^{c}
UIUT (0 mg/Kg)	1.15 ± 0.29^{a}	5.18 ± 0.90^{a}	0.90 ± 0.04^{b}	1.98 ± 0.30^{ab}	6.55 ± 1.27^{a}	2.48 ± 0.12^{b}
Male						
5 mg/Kg	0.57 ± 0.14^{a}	5.14 ± 0.83^{bc}	0.89 ± 0.08^{a}	1.95 ± 0.42^{bc}	5.28 ± 0.80^{b}	2.59 ± 0.66^{b}
45mg/Kg	0.55 ± 0.10^{a}	4.10 ± 0.30^{b}	0.88 ± 0.11^{a}	0.96 ± 0.25^{a}	5.85 ± 1.11^{b}	2.56 ± 0.33^{b}
90 mg/Kg	0.70 ± 0.31^{a}	3.87 ± 0.63^{b}	0.85 ± 0.04^{a}	1.61 ± 0.46^{ab}	4.28 ± 0.74^{b}	1.95 ± 0.29^{b}
Cipro (14 mg/Kg)	0.69 ± 0.14^{a}	2.10 ± 0.31^{a}	1.19 ± 0.04^{b}	1.49 ± 0.19^{b}	4.17 ± 0.65^{b}	1.61 ± 0.09^{b}
IUT (0 mg/Kg)	1.59 ± 0.09^{b}	6.26 ± 0.21^{c}	1.21 ± 0.15^{b}	5.47 ± 0.41^{d}	11.84 ± 2.72^{c}	3.73 ± 0.32^{c}
UIUT (0 mg/Kg)	0.65 ± 0.02^{a}	3.93 ± 0.32^{b}	0.92 ± 0.08^{a}	2.80 ± 0.65^{c}	3.13 ± 0.34^{a}	1.33 ± 0.07^{a}

The table values are presented as mean ± ESM of 4 repetitions. In the same column and for the same sex, the values bearing the different letters are significantly different ($p<0.05$). Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated

3.4.5 Effects of Treatment of Different Doses of Extract on Nitric Oxide (NO)

The variation of the nitric oxide level in the tissues and sera of female and male rats is presented in Table 7.

It appears that the infection resulted in a significant ($p<0.05$) decrease in nitric oxide levels in all organs and serum of female and male rats compared to neutral controls (UIUT).

The treatment resulted in a significant ($p<0.05$) increase in nitric oxide levels in almost all organs and serum of female rats and in the serum, heart, spleen, lung of male rats compared to negative controls (IUT). Furthermore, this NO level was not significant ($p \geq 0.05$) in the heart and kidneys of female rats at a dose of 5 mg/kg, and in the liver and kidneys of male rats compared to the same controls.

However, the treatment standardized ($p \geq 0.05$) at all the doses the NO level in all organs and serum of female rats and in the heart, liver, spleen, lungs of male rats as well as in serum and kidney of male rats at 90 mg/kg compared to neutral controls.

Table 7. Effects of treatment on nitric oxide (NO) levels in the blood and tissues of rats.

Sex and Doses	Organs and Quantity of Nitric Oxides (µmole/g of tissues and µmole/ml of blood)					
	Serum	Heart	Liver	Kidneys	Spleen	Lungs
Female						
5 mg/Kg	1.21 ± 0.29^{b}	0.06 ± 0.01^{ab}	0.16 ± 0.06^{b}	0.05 ± 0.03^{ab}	0.15 ± 0.00^{b}	0.15 ± 0.02^{bc}
45mg/Kg	1.26 ± 0.45^{b}	0.07 ± 0.00^{b}	0.11 ± 0.03^{b}	0.07 ± 0.01^{b}	0.15 ± 0.02^{b}	0.17 ± 0.01^{c}
90 mg/Kg	1.28 ± 0.06^{b}	0.07 ± 0.01^{b}	0.14 ± 0.00^{b}	0.08 ± 0.02^{b}	0.19 ± 0.01^{c}	0.14 ± 0.02^{bc}
Cipro (14 mg/Kg)	1.60 ± 0.32^{b}	0.07 ± 0.01^{b}	0.14 ± 0.01^{b}	0.06 ± 0.01^{b}	0.20 ± 0.02^{c}	0.13 ± 0.02^{b}
IUT (0 mg/Kg)	0.39 ± 0.01^{a}	0.04 ± 0.01^{a}	0.06 ± 0.01^{a}	0.03 ± 0.01^{a}	0.06 ± 0.01^{a}	0.07 ± 0.01^{a}
UIUT (0 mg/Kg)	1.16 ± 0.11^{b}	0.08 ± 0.01^{b}	0.12 ± 0.02^{b}	0.07 ± 0.01^{b}	0.15 ± 0.03^{bc}	0.15 ± 0.01^{bc}
Male						
5 mg/Kg	0.51 ± 0.05^{b}	0.10 ± 0.01^{b}	0.11 ± 0.02^{a}	0.06 ± 0.01^{a}	0.17 ± 0.02^{c}	0.12 ± 0.02^{b}
45mg/Kg	0.66 ± 0.10^{b}	0.13 ± 0.04^{b}	0.11 ± 0.01^{a}	0.07 ± 0.01^{a}	0.11 ± 0.02^{b}	0.13 ± 0.01^{b}
90 mg/Kg	1.08 ± 0.16^{c}	0.11 ± 0.01^{b}	0.12 ± 0.00^{a}	0.12 ± 0.04^{ab}	0.16 ± 0.02^{c}	0.14 ± 0.03^{b}
Cipro (14 mg/Kg)	0.60 ± 0.16^{ab}	0.12 ± 0.02^{b}	0.22 ± 0.04^{b}	0.12 ± 0.02^{b}	0.12 ± 0.01^{b}	0.13 ± 0.01^{b}
IUT (0 mg/Kg)	0.40 ± 0.03^{a}	0.07 ± 0.01^{a}	0.08 ± 0.03^{a}	0.07 ± 0.02^{a}	0.07 ± 0.01^{a}	0.07 ± 0.01^{a}
UIUT (0 mg/Kg)	1.03 ± 0.09^{c}	0.11 ± 0.02^{b}	0.23 ± 0.05^{b}	0.10 ± 0.01^{b}	0.13 ± 0.02^{bc}	0.17 ± 0.05^{b}

The table values are presented as mean ± ESM of 4 repetitions. In the same column and for the same sex, the values bearing the different letters are significantly different ($p<0.05$). Cipro: ciproflaxacin; IUT: Infected and untreated; UIUT: Uninfected and untreated.

4. Discussion

4.1 *In vivo* Antisalmonellal activity

Salmonella Typhi infection induces several physiological changes in animals such as excretion of liquid stools, reduction of its activity, exponential increase of *Salmonella* in blood, presence of blood and mucus in the stool (Fodouop *et al.*, 2014) [14]. After administration of the infectious load, a latent period of 24 hours during which there was no significant increase of colonies in the blood of the rats was observed. This period corresponds to the time of acclimation of the bacteria to the new conditions of the medium, thus the bacterium is internalized, disperses and multiplies in the non-specific defense cells of the rats (Ellermeier and Slauch, 2006) [12]. The exponential increase in the number of *Salmonella Typhi* in the blood ($\geq 4 \times 10^5$ CFU/ml) in rats after the latency phase is indicative of the establishment of the infection. This period corresponds to a critical density of bacteria that causes the apoptosis of these cells, thus finding the blood system in large numbers and then invading the rest of the body of rats as in infected and untreated rats.

The decrease in this bacterial load observed after the start of treatment could be due to the combined action of the extract and the immune system, since a slight phase of decline was observed in the infected and untreated animals. (Kodjio *et al.*, 2016) [4, 17].

Rats treated with different doses of extract were practically free of salmonella between the eighth and twelfth day of treatment. The male rats were cured dose-dependent from the eighth day while the female rats were cured from the tenth day. These differences observed in the recovery of rats after treatment are due to the individual physiological behavior of each rat during infection and treatment with the extract (Ngoudjou *et al.*, 2017).

The leaf extract of *Adenia lobata* revealed the presence of bioactive compounds such as flavonoids, alkaloids, steroids, tannins, phenols, saponins, anthocyanins, triterpenes and anthraquinones. This is similar to the work of Agoreyo *et al.* (2012) [2], who had already demonstrated the presence of some of these compounds in the methanol leaf extract of *Adenia lobata*. Several studies have already demonstrated the antibacterial activities of some bioactive compound.

Daily administration of leaf extract of *Adenia lobata* during treatment caused at all doses an increase in food consumption in rats. Plant extracts by their constitutions may have several nutrients that would justify the weight gain of rats during treatment. Nevertheless, the infection did not generally damage the organs of the rats.

However, during a salmonella infection there is production of reactive oxygen species that can interact with each other and cause oxidative stress.

4.2 *In vivo* antioxidant activity

Reactive oxygen species (ROS) are oxidants formed in our body due to exogenous and endogenous factors. These ROS are thought to be responsible for many diseases such as cancer, cardiovascular diseases, neurodegenerative diseases, inflammatory diseases, and aging (Cohen *et al.*, 2000) [8].

During microbial infection, the free radicals generated can bind and alter cellular molecules such as glucose, DNA, proteins and lipids (Raucy *et al.*, 1993) [24]. Thus, to counter the deleterious effects of these free radicals and to prevent oxidative stress, the body sets up antioxidant systems (superoxide dismutase, glutathione, and catalase) to restore equilibrium.

Superoxide dismutases (SOD) are the first line of antiradical defense and catalyze the dismutation of the superoxide anion into oxygen and hydrogen peroxide. Their action is coupled with that of enzymes that degrade hydrogen peroxide, such as catalases (Vergely and Rochette, 2003) [31], which protect cells against the accumulation of H_2O_2 by disintegrating it to form H_2O and O_2 (Bhakta *et al.*, 1999) [5]. In the present study, the infection resulted in a significant ($p<0.05$) decrease in SOD and catalase activity in almost all organs and sera of animals of both sexes compared to uninfected and non-infected controls. Decreased activity of these enzymes in infected and untreated rats is a sign of oxidative damage (Kumar *et al.*, 2010) [19]. Salmonella infection would therefore cause a significant change in cellular redox status in favor of reactive oxygen species (Adaramoy *et al.*, 2008; Akomolafe *et al.*, 2011) [1, 3]. The inactivation of SOD and catalase may be due to their permanent presence (Wassmann *et al.*, 2004) [32]. The significant ($p<0.05$) and non significant increase in SOD and catalase activities in the tested rats, compared to infected and untreated controls, is an evidence of suppression or inhibition of oxidative stress induced by *S. Typhi*. The extract would therefore contain antioxidant substances that neutralize the reactive oxygen species, thus preventing the inactivation or destruction of SOD and catalase by promoting the protection of these organs against any tissue damage induced by these reactive compounds. The results of this study are similar to those obtained with extracts of *Albizia gummifera* (Atsafack *et al.*, 2016) [17], *Curcuma longa* (Kodjo *et al.*, 2016) [17].

Reduced glutathione (GSH) is an integral part of the first line of antiradical defense. It is the body's most effective detoxifying agent, regulating and regenerating immune cells (Raja *et al.*, 2007) [23]. Glutathione peroxidases reduce hydrogen peroxide to water through reduced glutathione/glutathione disulfide (Vergely and Rochette, 2003) [31]. A significant decrease ($p<0.05$) in untreated typhoid rats is indicative of GSH deficiency due to high production of reactive oxygen species, and therefore low defense capacity of the anti-radical system (Haleng *et al.*, 2006) [16]. The significant ($p<0.05$) increase in glutathione levels in the serum, liver, and spleen of the treated rats compared to the untreated and infected controls, indicates that the hydroethanolic extract of *A. lobata* has plant antioxidants that can stimulate the body's antioxidant system, reducing unstable peroxides.

Malondialdehyde (MDA) is a marker of oxidative damage used to assess lipid peroxidation in tissues. It is one of the final products in the oxidative degradation of polyunsaturated fatty acids of the cell membrane (Sharida *et al.*, 2012) [27]. In the present study, infection resulted in a significant ($p<0.05$) increase in malondialdehyde in both sexes compared to neutral controls (UIUT). This increase could be due to a rise in reactive oxygen species on the antioxidant system of the body thus causing a state of oxidative stress. Administration of the hydroethanolic extract of *A. lobata* in animals significantly reduced ($p<0.05$) the level of MDA in tissues and serum compared to infected and untreated animals (IUT) and normalized this MDA level in almost all organs and sera of rats compared to uninfected and untreated animals (UIUT). The extract would therefore prevent the destruction of the membrane bilayer of cells by neutralizing free radicals like hydrogen peroxides (H_2O_2) and the hydroxyl radical (OH •) known for their ability to produce tissue peroxidation of cells by simultaneous etching of polyunsaturated fatty acids (Dharmendra *et al.*, 2014) [10].

Macrophages produce nitric oxide (NO) through the action of inducible nitric oxide synthase which metabolizes arginine to citrulline and NO. Nitric oxide is involved in a dynamic process by macrophages to destroy salmonella (Vazquez-Torres *et al.*, 2000) [30]. In this study, the significant ($p<0.05$) decrease in nitric oxide levels in *S. Typhi*-infected and untreated rats compared to neutral controls may be due to massive destruction of defense cells (macrophages) of rats due to *Salmonella Typhi*. The increase in NO level after treatment in tested rats compared to infected and untreated rats could be due to the combined action of the extract and the organism. The hydroethanolic extract of *A. lobata* could have stimulated the host's organism to produce the macrophages involved in the destruction of salmonella. The phytochemical composition of this extract reveals the presence of phenolic compounds and the antioxidant potential of these bioactive compounds has already been demonstrated.

5. Conclusion

The results presented in this work show that, the hydroethanolic leaves extract of *Adenia lobata* can treat and completely cure typhoid fever from the 5 mg/kg dose and reduce the state of oxidative stress caused by infection of *Salmonella Typhi*. However, further studies should be conducted to define the therapeutic dose that would allow the safety of its use.

6. Acknowledgments

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7. Ethical guidelines

During the treatment, experimental animals were treated in accordance with the ethical guidelines of Committee for Control and Supervision of Experiments on Animals (Registration no. 173/ CPCSEA, dated 28 January, 2000), Government of India, on the use of animals for scientific research.

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