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Annals of Reproductive Medicine and Treatment

Research Article

Protective Effect of *Zanthoxyliun leprieurii* Fruits on Reproductive Organ Weight and Serum Metabolite Profile, Testicular Structure and Function Impairment in Male Cavy (*Cavia porcellus*) Exposed to Hyperthermia

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Submitted: 05 June 2020

Accepted: 18 June 2020

Published: 20 June 2020

ISSN: 2573-1092

OPEN ACCESS

Keywords

- Male guinea pig
- Reproduction
- Hyperthermia
- *Zanthoxylium leprieurii*

Abstract

The present work was carried out in order to evaluate the effects of high temperature in male guinea pig (*Cavia porcellus*) reproductive characteristics and mitigation strategy using aqueous extract (AE), of *Zanthoxylium leprieurii* fruits. For this purpose, seventy-two (72), adult male guinea pigs aged about 4 months and weighing between 350-400 g were divided into 6 groups of 12 guinea pigs each, comparable in terms of body weight (bw). The six group were randomly subjected to the treatments as follow: T0 (neutral control co-exposed to 20-25°C + 2 ml/kg bw of distilled water); T0- (negative control), T0+ (positive control), AE100, AE200 and AE400 were all exposed to temperature at 46 ± 1 °C and respectively received distilled water (2 ml/kg bw), vitamin C (200 mg/kg bw); 100, 200 and 400 mg/kg bw aqueous extract of *Z. leprieurii*). The exposure time was 6 hours per day for 60 days. At the end of the trial, samples were collected for analysis of reproductive characteristics. Results showed that serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone ; the weight of testes and vas deferens, the epididymal sperm mobility and density were significantly ($p<0.05$) greater in heat stressed guinea pigs treated with vitamin C and *Z. leprieurii* AE at 200 and 400 mg/kg bw compared to negative control (T0-). Serum Heat Shock Protein (HSP), concentrations were significantly ($p<0.05$) higher (82.27 ± 1.63 ng/ml), in heat-stressed guinea pigs treated at 400 mg/kg bw of AE compared to negative control (T0-) (43.01 ± 1.34 ng/ml). In conclusion, the oral administration of *Z. leprieurii* fruit aqueous extract reduced the negative impact of elevated temperatures in male guinea pig reproductive characteristics.

INTRODUCTION

According to the Intergovernmental Conference report on Climate Change [1], the Earth's temperature is increasing by around 0.2°C per decade. In the year 2100, it would have increased from 1.4 to 5.8°C. According to Hansen [2], and Emtnan et al. [3], the increase in temperature, greatly affect reproductive performance in mammals. Ambient temperatures above 20-25°C in the temperate zone and 25-37°C in the tropical zone are sensitive to induce oxidative stress in animals [4,5]. Heat stress resulting from high temperature disrupts homeostasis. It negatively affects the semen quality and quantity, the testis structure and function [6]. These effects subsequently induce sub-fertility and infertility [7].

Thermal shocks both high temperatures and low temperatures are the causes of an overproduction of oxygen reactive species in which free radicals [8]. According to Kumar and Gandhi [9], high temperature creates an imbalance between the activated oxygen reactive species and the antioxidant defense system. This imbalance favors the accumulation of free radicals which cause lipid peroxidation and consequently the deterioration of reproductive performance [10]. Several studies have reported that an increase (acute or chronic) in testicular temperature adversely affects spermatogenesis, resulting in a decrease of the density of spermatozoa [11-13]. As a solution, the antioxidant capacities of animals can be enhanced by nutritional supplements such as vitamins A, E and C and some minerals including Selenium and Zinc [9]. On the other hand, study on some plants and plant

by-products, showed that they have molecules with antioxidant properties which can be used in animal production neutralize the negative effects of high temperatures. This is the case of green tea extracts [14], aqueous extracts of guava leaves [15], and essential oil of guava leaves [16]. The same properties are also founded in several spices such as *Zanthoxylum leprieurii* which is used to boost food flavor [17].

Zanthoxylum leprieurii is one of the spice plants commonly used in Central and West Africa for traditional medicine. Root and bark decoctions are said to have excellent diuretic and purgative activities [18]. They are also used as analgesics and against heart palpitations [19]. The *Z. leprieurii* is rich in various bioactive molecules (phenols, flavonoids, tannins, terpenoids and saponins). These molecules possess diverse biological properties including antioxidant activity [20], which can be used in animal production to limit the oxygen reactive species attacks. This study was designed to test the protector effects of *Z. leprieurii* fruit aqueous extract on genital organs weight and histopathological changes, sperm characteristics, serum level of reproductive hormones and HSPs in heat- stress male guinea pigs.

MATERIALS AND METHODS

Collection and preparation of *Z. leprieurii* fruit aqueous extract

The seeds of *Zanthoxylium* were bought from Dschang (Menoua division in Cameroon), local market. They were dried sheltered from the sun, and then ground at the mill. The obtained powder was used for extractions, using 6 liters of distilled water for 1 kilogram of powder. The filtrate was dried in the oven at 45°C to obtain a paste used to prepare the *Z. leprieurii* aqueous extract at different concentrations.

Experimental animals and design

Seventy-two male cavies (*Cavia porcellus*) weighing 330.56 ± 23.62g, with average age of 3-4 months were used. The cavies were reared in the Teaching and Research Farm of the University of Dschang (Cameroon). They were identified using numbered earrings and housed in identical cages of dimensions 100 cm ×80 cm × 60 cm (length, width and height) under 12 hours' light/day and had free access to feed and water.

Animals were divided into six groups of twelve animals each, randomly assigned in terms of body weight. They were subjected to the following treatments: T0 (neutral control): 20-25 °C + 2 ml/kg bw of distilled water and T0- (negative control), T0+ (positive control), AE100, AE200 and AE400. Animals from T0- to AE400 were all exposed to 46 ± 1°C and respectively received distilled water (2 ml/kg bw), vitamin C (200 mg/kg bw); 100, 200 and 400 (mg/kg bw AE from *Z. leprieurii*). The exposure time was 6 hours per day for 60 days.

Data collection

Twenty-four hours after the last exposure to heat and administration of doses of vitamin C and *Z. leprieurii* fruit aqueous extract, each animal was anesthetized using ether vapor and blood samples were collected by cardiac puncture for determination of hormone levels and HSP-40. Thereafter, animal were sacrified, testes, epididymides, vas deferens and sexual accessory glands were excised and weighed. The cauda epididymides were weighed and immersed in 5 ml 0.9% NaCl solution (37 °C), for sperm characteristics. Briefly, a drop of the latter solution was placed on a slide, observed at 40X magnification under the microscope and sperm mobility examined as reported by Boiti et al. [21]. Sperm count was done using the Thomas haemocytometer. Briefly, defined aliquots of the sperm was dissolved and immobilized in 10 % Formol/NaCl solution. After gentle stirring of the sample, spermatozoa were counted microscopically using hemacytometer chamber in a total of 10 square out of two chamberfields.

Evaluation of reproductive hormones and Heat Shock Protein (HSP)

Serum levels of testosterone, FSH and LH were measured using ELISA kit from Omega Diagnostics (Scotland, United Kingdom). HSP levels in serum samples were determined using guinea pig Heat Shock Protein 40 (HSP-40) ELISA kit (ABclonal Biotechnology Co., Lto China), as per instructions from the manufacturer.

Histology

The right testis was fixed by immersion in 10% NaCl solution for 1 week and then washed, dehydrated in ascending grade alcohol bath, clarified in xylene immersion, and embedded in paraffin. Sections of 5µm were stained with hematoxylin–eosin for histological observations under a light microscope (400×).

Statistical analysis

Data were analyzed using SPSS IBM statistics software 20.0. Differences between groups were assessed using one-way analysis of variance (ANOVA), and specific differences between pairs of means assessed by Duncan's test at 5% significance.

RESULTS

Effects of *Z. leprieurii* on reproductive organ weights in male guinea pig exposed to high temperature

Table 1 summarizes the effects of the *Z. leprieurii* fruit aqueous extract on the weight of genitals organs in male guinea pig subjected to heat stress. The relative weights of the testes, accessory glands and vas deferens decreased significantly ($p<0.05$), in heat stressed animals compared to the neutral control. In addition, the relative weight of the epididymis decreased non-significantly ($p>0.05$) in heat stressed animals compared to the neutral control. The administration of *Z. leprieurii* fruit aqueous extract at doses of 200 and 400 mg/kg bw induced a significant increase ($p<0.05$) of the weight of the testes, accessory glands and vas deferens compared to thermal stress exposed animals (T0-).

Effect of *Z. leprieurii* on reproductive hormones in male guinea pig exposed to high temperature

It appears that the concentrations of FSH, LH and testosterone decreased significantly ($p <0.05$), in guinea pigs subjected to heat stress compared to neutral controls. The administration of *Z. leprieurii* fruit aqueous extract whatever the dose and vit

Table 1: Effects of *Z. leprieurii* fruit aqueous extract on the relative weight of genitals organ in heat stressed male guinea pig.

Relative weight of genital organs (g/100 g bw)	Controls			Doses of *Z. leprieurii* AE (mg/kg bw)			P Values
	T0 (n=12)	T0- (n=12)	T0+ (n=12)	100 (n=12)	200 (n=12)	400 (n=12)	
Testis	0.43±0.01b	0.31±0.01e	0.39±0.01c	0.36±0.02d	0.41±0.01bc	0.51±0.02a	0
Epididymis	0.09±0.03	0.07±0.01	0.08±0.01	0.07±0.02	0.08±0.02	0.09±0.01	0.56
Accessory glands	0.34±0.02c	0.22±0.03d	0.45±0.03b	0.24±0.01d	0.54±0.01a	0.34±0.01c	0
Vas deferens	0.04±0.01b	0.03±0.01c	0.05±0.01a	0.03±0.01c	0.05±0.01a	0.05±0.01a	0

n= number of guinea pigs. (a, b, c, d, e): on the same line, the values affected by the same letter do not differ significantly (p>0.05). bw: body weight. p = probability. T0 = Neutral control (20-25 ° C + 2 ml / kg bw of distilled water). T0- = Negative control (46 ± 1 ° C + 2 ml / kg bw of distilled water). T0 + = Positive control (46 ± 1 ° C + 200 mg / kg bw of VC). AE100, AE200, AE400 = aqueous extract (mg / kg bw) + Temperatures (46 ± 1 ° C). VC: vitamin C.

Table 2: Effects of *Z. leprieurii* fruit aqueous extract on serum reproductive hormones in heat stressed male guinea pig.

Hormones concentrations	Controls			Doses of Z. leprieurii AE (mg/kg bw)			
	T0 (n=12)	T0- (n=12)	T0+ (n=12)	AE100 (n=12)	AE200 (n=12)	AE400 (n=12)	*P values*
FSH (mUI ml-1)	8.68±0.06d	5.67±0.05f	6.43±0.16e	9.79±0.05b	9.61±0.10c	10.59±0.06a	0
LH (mUI ml-1)	1.09±0.02bc	0.98±0.02cd	1.38±0.01a	1.23±0.27ab	1.33±0.04a	0.85±0.07d	0
Testostérone (ng ml-1)	0.55±0.02b	0.38±0.03c	0.43±0.02c	0.42±0.01c	1.27±0.06a	0.55±0.04b	0

n = number of guinea pigs. (a, b, c, d, e, f): on the same line, the values affected by the same letter do not differ significantly (p>0.05). bw: body weight. p = probability. T0 = Neutral control (20-25 ° C + 2 ml / kg bw of distilled water). T0- = Negative control (46 ± 1 ° C + 2 ml / kg bw of distilled water). T0 + = Positive control (46 ± 1 ° C + 200 mg / kg bw of VC). AE100, AE200, AE400 = aqueous extract (mg / kg bw) + Temperatures (46 ± 1° C). VC: vitamin C.

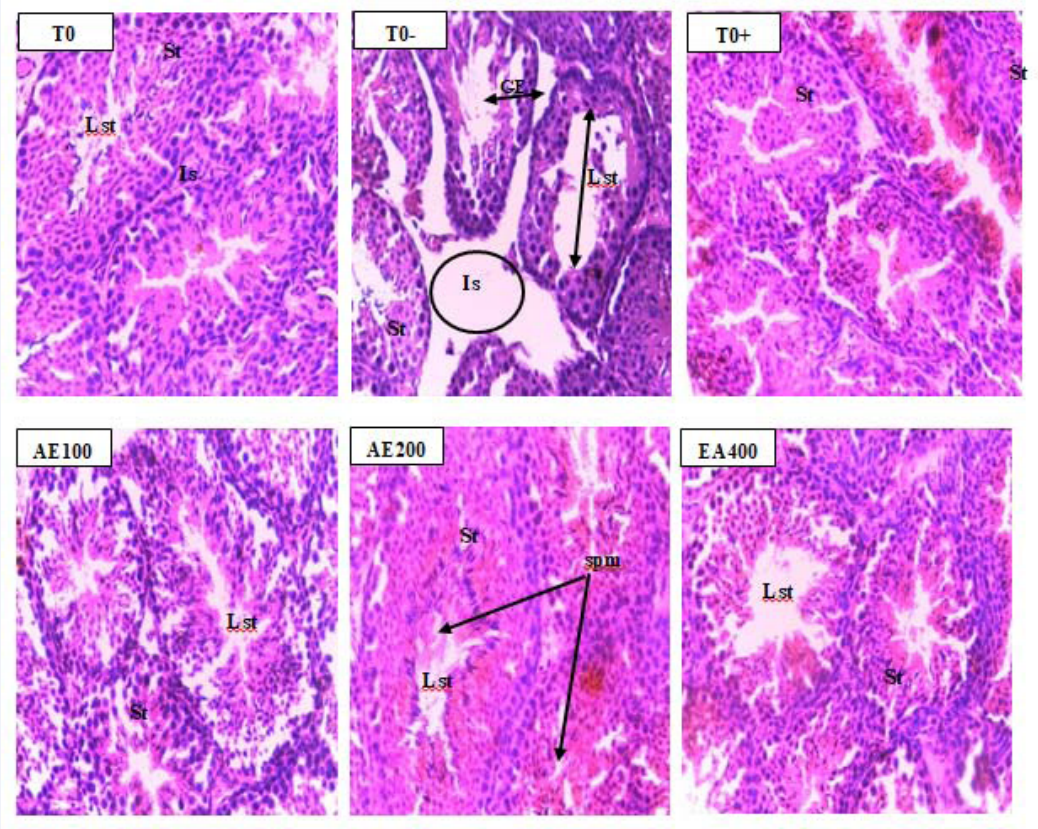

Figure 1 Histological structures of testes in guinea pigs exposed to thermal stress and treated with *Z. leprieurii* fruit aqueous extract (HE x 400).

St: seminiferous tube; Lst: lumen of the seminiferous tube; Is: interstitial space; Spm: sperm; GE: Germinal epithelium.T0 = Neutral control (20-25 ° C + 2 ml / kg bw of distilled water); T0- = Negative control (46 ± 1 ° C + 2 ml / kg bw of distilled water); T0 + = Positive control (46 ± 1 ° C + 200 mg / kg bw VC); AE100, AE200, AE400 = aqueous extract (mg / kg bw) + Temperatures (46 ± 1 ° C); VC: vitamin C; bw: body weight.

C led to a significant increase (p<0.05), in FSH compared to the negative controls (T0-). For LH, the increase was significant (p<0.05), only with vit C and *Z. leprieurii* fruit aqueous extract at 100 and 200 mg/kg bw. With respect to negative controls (T0-), the *Z. leprieurii* fruit aqueous extract at 200 and 400 mg/kg bw significantly increased the serum content in testosterone.

Effect of *Z. leprieurii* on sperm characteristics in guinea pig exposed to high temperature

Table 3 presents the effects of *Z. leprieurii* fruit aqueous extract on the characteristics of epididymal spermatozoa in the male guinea pig subjected to heat stress. It shows that the mobility, concentration and membrane integrity of the sperm decreased significantly (p <0.05), in guinea pigs subjected only to thermal stress compared to neutral controls. With respect to negative control, the vitamin C and *Z. leprieurii* fruit aqueous extract whatever the dose considered led to a significant increase (p <0.05), of these sperm characteristics.

Histological structure of the testes

Figure 1 illustrates the effects of *Z. leprieurii* fruit aqueous extract on testicular structures in male guinea pigs subjected to thermal stress. In neutral control animals (T0), the architecture of the seminiferous tubes was normal. From the membrane to the lumen of the tubes, germ cells are observed at different stages of development. The lumen of the tubes contains many mature sperms. This cellular arrangement was disturbed in the T0- (negative control), guinea pigs where the lumen of the seminiferous tubes and the interstitial spaces showed degradation of the various cells. In heat stressed cavies treated with *Z. leprieurii* fruit aqueous extract or vitamin C, the absence of anomaly noted in negative control was recorded. Briefly, the seminiferous tubes were more structured and there were mature germ cells in the lumen.

Effect of Z. leprieurii and *Z. leprieurii* fruit aqueous extract on Heat Shock Protein in male guinea pig exposed to heat stress

Figure 2 illustrates the variation in the serum concentration of HSP 40 in animals subjected to heat stress and treated with *Z. leprieurii* fruit aqueous extract. It appears that the serum concentration of HSP 40 significantly (p <0.05) decreased in the animals subjected to heat stress compared to the neutral controls. The oral administration of vit C and *Z. leprieurii* fruit aqueous extract at doses of 200 and 400 mg / kg bw resulted in a significant increase (p <0.05) in the serum level of HSP 40 compared to the negative control. However, these values remain significantly (p <0.05) lower than those recorded in the neutral controls.

DISCUSSION

In this study, the impact of heat stress on reproductive parameters in male guinea pigs and its mitigating strategies were assessed. The study of Roy et al. (2016), revealed an exposure of animals to heat stress causes testicular damage and subsequently affects their reproductive performances [22]. In the present study, the weights of the reproductive organs were lower in the heat stressed animals compared to the neutral control (T0). These results corroborate those of Yangli et al. [23], in the male rabbit exposed between 26 and 36 °C for 9 weeks, and Ngoula et al. [16], in the male guinea pig exposed to 45°C during 06 hours per day for 60 days. The exposure of animals to heat stress leads to an overproduction of reactive oxygen species (ROS) which denature DNA and impair the testicular cell membranes. This effect is associated to cell death and low testes weights. The gonads are mostly made up of germ cells [24]. The drop in testicular weight observed in the present work can be associated with that of the number of germ cells.

Testosterone is an important androgen produced by Leydig cells in the testicle under the control of LH (pituitary hormone). In the present study, a significant drop in serum testosterone, LH and FSH concentrations was recorded in guinea pigs exposed at 46 ± 1°C. These results are similar to those of Roy et al. [22], in albino rats exposed to 43°C, 30 min per day for 14 days; and Emtenan et al. [3], in rats exposed to 42°C, 4 hours a day for 08 weeks. In the situations of heat stress, the activity of testosterone remains low, thus indicating a deficiency in the secretory function of Leydig cells and the maturation of spermatozoa in the epididymis [25,26]. Research of testicular histopathology carried out through this study revealed damages such as the disintegration of the seminiferous tubes and interstitial cells in the guinea pig exposed to heat stress. Since the Leydig cells are located in the testes interstitial space, the negative effects of hyperthermia in testes area would positively correlated with impairment of the Leydig cells function as it noted in this study. Such observations were also also reported by Roy et al. [22], in albino rats exposed to 43°C, 30 min per day for 14 days.

The administration of 200 or 400 mg/kg bw of the *Z.*

Table 3: Effects of *Z. leprieurii* fruit aqueous extract on the characteristics of epididymal spermatozoa in the male guinea pig subjected to heat stress.

Caudal epididymal sperm characteristics		Controls		Doses of Z. leprieurii AE (mg/kg bw)			
	T0 (n=12)	T0- (n=12)	T0+ (n=12)	AE100 (n=12)	AE200 (n=12)	AE400 (n=12)	P valu es
Mobility (%) Number/	73.33±0.58c	23.33±0.58f	55.02±0.91e	66.33±0.58d	85.02±0.00a	79.25±0.96b	0
cauda epididymis (x107)	6.19±0.37b	2.11±0.14d	4.63±0.32c	4.52±0.18c	6.25±0.35ab	6.67±0.38a	0
Number/g of epididymal tail (x106)	42.24±0.35b	15.21±0.21f	23.22±0.58e	46.38±0.46a	27.66±0.63d	34.95±0.23c	0
Membrane integrity	66.75±0.51b	19.25±0.87e	52.51±0.58d	55.25±0.65c	75.02±0.86a	65.22±0.84b	0

n = number of guinea pigs. (a, b, c, d, e, f): on the same line, the values affected by the same letter do not differ significantly (p>0.05). bw: body weight. p = probability. T0 = Neutral control (20-25 ° C + 2 ml / kg bw of distilled water). T0- = Negative control (46 ± 1 ° C + 2 ml / kg bw of distilled water). T0 + = Positive control (46 ± 1 ° C + 200 mg / kg bw of VC). AE100, AE200, AE400 = aqueous extract (mg / kg bw) + Temperatures (46 ± 1° C). VC: vitamin C.

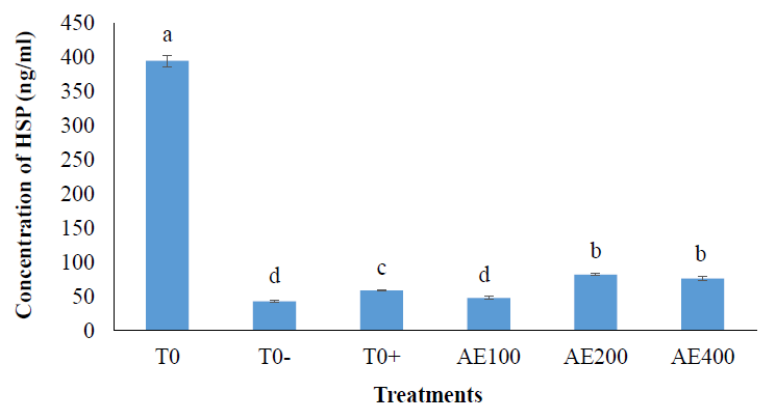

Figure 2 Effects of *Z. leprieurii* fruit aqueous extract on the serum concentration of HSPs in the male guinea pig subjected to heat stress. (a, b, c, d): on the same histogram, the bars affected by the same letter do not differ significantly (p>0.05). T0 = Neutral control (20-25 ° C + 2 ml / kg bw of distilled water). T0- = Negative control (46 ± 1 ° C + 2 ml / kg bw of distilled water). T0 + = Positive control (46 ± 1 ° C + 200 mg / kg bw VC). AE100, AE200, AE400 = aqueous extract (mg / kg bw) + Temperatures (46 ± 1 ° C). VC: vitamin C. bw: body weight.

leprieurii fruits aqueous extract heat stressed animals resulted in a significant increase in the weight of the genital organs and the serum concentrations of reproductive hormones. These results are similar to those obtained by Emtenan et al. [3], and Roy et al. [22], in rats, treated with the aqueous extract of *Ferula hermosis* at the dose of 0.025 ml /100 g bw, and the methanolic extract of *Mallotus roxburghianus* at the dose of 400 mg/kg, respectively. These observations can be explained by the action of antioxidant compounds such as phenols, flavonoids, tannins, terpenoids and saponins present in the *Z. leprieurii* fruit aqueous extract. According to Hodek et al. [27], molecules with antioxidant properties neutralize free radicals or inhibit the enzymes responsible for their production. This effect protects animal cells including testis cells against reactive oxygen species attacks and increases their size and their secretory function [28]. In the other hand, Androgens and more particularly testosterone have anabolic properties characterized by the increase in protein synthesis and consequently the increase in muscle mass. One of the roles of androgens is to increase the volume and weight of the testis and epididymis by stimulating protein synthesis [29]. The increase in testosterone concentration recorded following the administration of the aqueous extract in this study would induce the elevated weight of reproductive organs.

The density and mobility of sperm are considered to be the interesting sperm characteristics in animals to evaluate it fecundity [30]. The results of this work have shown a decrease in sperm concentration, mobility and membrane integrity in male cavies exposed to heat stress. These results are similar to those reported by Mishra et al. [31], in bulls (jersey), subjected to high temperature levels (25-35°C; 35°C and more), Abshenas *et al.* [14] in mice whose scrotum was subjected to heat stress at 42°C. Heat stress affects both mobility and density of spermatozoa [2,32], and induces azoospermia or oligospermia in animals [11]. In this study, the decline in sperm characteristics would be the result of disintegration of the plasma membrane and DNA of the sperm as a consequence of ROS attacks. Indeed, the plasma membrane of sperm is rich in polyunsaturated fatty acids [33, 34]. These characteristics make them vulnerable to radical attacks.

In the present work, the administration of the *Z. leprieurii* fruit aqueous extract at 100, 200 or 400 mg/kg bw protects the membrane of the spermatozoa, but also an increase in sperm concentration and mobility in heat stressed animals. These results corroborate those of Abshenas et al. [14], in mice subjected to 42°C for 49 days and treated with methanolic extract of *Camellia sinensis* at doses of 500 and 750 mg/kg bw. These effects observed in the present study is linked to the *Z. leprieurii* bioactive molecules with antioxidant properties, which have reduced or prevented the attacks of sperm by free radicals.

Hyperthermia induces the synthesis of "heat shock proteins" (HSP), most of which are chaperone molecules which are normally overexpressed by cells in response to inducible signals which can lead to proteins denaturation [35]. However, at a certain degree of temperature (generally from 42°C), there is inhibition of the synthesis of HSPs with the main consequence of an exponential increase in cellular apoptosis [36]. Exposure of the animals to 46°C revealed a significant drop in the serum concentration of HSPs 40. The administration of the *Z. leprieurii* fruit aqueous extract at 200 and 400 mg/kg bw concomitantly with the exposure of animals to 46 ºC considerably reduced the influence of heat stress on the serum concentrations of HSPs 40. This effect would result of the antioxidant property of the *Z. leprieurii* fruit aqueous which have reduced the stress in hyperthermia situation and subsequently avoid the cell deterioration.

CONCLUSION

The results of this study revealed that heat stress caused impairment of reproductive characteristics in male cavies, illustrated by markedly impairment in the testes structure and sperm characteristics, decreased of reproductive hormone concentrations and serum concentration of Heat Shock protein 40. The administration of *Z. leprieurii* fruit aqueous extract efficiently improved cavy reproductive characteristics. Based on these effects, the *Z. leprieurii* fruit aqueous extract at 200 and 400 mg/kg bw can be used in male animals to improve its reproductive performances.

ETHICS STATEMENT

All experiments were carried out in compliance with the recommendations Guide of the National Academy of Sciences on the care and use of laboratory Animals (NAS, 2013), and approved by the department of animal science.

FUNDING

The authors received no funding from an external source.

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Cite this article

Aime LF, Narcisse VB, Herve T, Dorice AK, Nadege DM, et al. (2020) Protective Effect of Zanthoxyliun leprieurii Fruits on Reproductive Organ Weight and Serum Metabolite Profile, Testicular Structure and Function Impairment in Male Cavy (Cavia porcellus) Exposed to Hyperthermia. Ann Reprod Med Treat 4(1): 1022.