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Effect of Ginger and L-Carnitine on the Reproductive Performance of Male Rats

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***Abstract*—**In this study, we investigated the effects of ginger and L-carnitine on the reproductive performance of male rats with respect to semen parameters, male sex hormones and the testicular antioxidant system. A total of sixty mature male albino rats were divided into four groups of fifteen rats. The control group received saline, whereas the other three groups received ginger (100 mg kg^{-1} d^{-1}.), L-carnitine (150 mg kg^{-1} d^{-1}.) or a combination of both ginger (100 mg kg^{-1} d^{-1}.) and L-carnitine (150 mg kg^{-1} d^{-1}.) via a stomach tube daily for one month. At the end of the treatment period, the rats were sacrificed, and their sperm characteristics (count, motility and viability), antioxidant enzyme factors levels (reduced glutathione, catalase, superoxide dismutase and total antioxidant capacity) and sex hormone levels (testosterone, Follicle stimulating hormone(FSH) and luteinizing hormone (LH) were analysed. Our results showed that the three experimental treatments improved sperm parameters, antioxidant enzyme activity and testosterone hormone levels; the most pronounced positive effects were observed in the group that received a combination of both ginger and L-carnitine. Therefore, the administration of a combination of ginger and L-carnitine may be beneficial for improving male sexual performance.

***Keywords*—**Ginger, L-Carnitine, Spermatogenesis, Rats.

I. Introduction

THE use of ginger (Zingiber officinale Roscoe), and specifically its medicinally active rhizome, has gained popularity among modern physicians in recent years [1] The pharmacological effects of ginger and its fresh and dried rhizome, including its anti-platelet, antioxidant, anti-tumour, anti-rhinoviral, anti-hepatotoxic and anti-arthritic activities, have been demonstrated [2]. Ginger extracts have also been reported to have a potent androgenic activity in male rats [3]

L-carnitine is a conditionally essential amino acid that plays an important role as a cofactor in cellular energy production in the mitochondrial matrix. L-carnitine aids in the transport of activated acyl groups across the mitochondrial inner membrane, and it is needed for the oxidation of long-chain fatty acids in the mitochondria of all cells [4].

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L-carnitine exhibits a wide range of biological activities including anti-inflammatory [5], cardioprotective [6], gastroprotective [7], antiapoptotic and neuroprotective properties [8].

In several experimental and clinical studies on groups of patients with idiopathic oligoasthenospermia, the total carnitine level in their seminal plasma was found to be low, and oral L-carnitine supplementation resulted in improved sperm motility [9].

II. Materials and Methods

A. Experimental Animals

A total of sixty apparently healthy adult male albino rats that initially weighed approximately 85 g were used in this study. The animals were purchased from a laboratory animal facility in Tanta, Egypt, and were housed at the Department of Physiology in the Faculty of Veterinary Medicine at Damanhour University. The rats were acclimatised for one week. They were kept in cages with five rats per cage in a controlled environment that was maintained under a 12 hour light/dark cycle, a temperature of 24°C (±3°C) and 50-70% humidity. The rats were supplied with a standard diet and water ad-libitum.

B. Plants andChemicals:

1. Ginger

Ginger was purchased from MEPACO-MEDIFOOD, which is an Arab company that supplies pharmaceuticals and medicinal plants (Enshas, Sharkey, Egypt), in the form of 30 tablets that each contained 400 mg of ginger (fine powder). The ginger was dissolved in a physiological saline solution and was orally administered each day via a stomach tube at a dose of 100 mg/kg body weight [10].

2. L-Carnitine

L-Carnitine was also purchased from MEPACO-MEDIFOOD in the form of syrup (300 mg/ml L-carnitine). The L-carnitine syrup was diluted in a physiological saline solution and was orally administrated each day via a stomach tube at a dose of 150 mg/kg body weight [11].

C. Preparation of Ginger and L-carnitine Solutions

All rats were weighed once per week to calculate the average weight for each treatment; these weights were used to determine the required amount of ginger or L-carnitine and the

volume of saline solution. The doses were then prepared according to the following procedures.

1. Ginger

A ginger tablet was ground in a porcelain mortar and dissolved in the appropriate volume of saline to obtain the calculated dose.

2. L-Carnitine

The required volume of L-carnitine was diluted in the appropriate volume of saline to obtain the calculated dose.

D. Experimental Design

A total of sixty rats were designated into four groups (15 rats each). The control group received saline, whereas the other three groups received ginger (100 mg/kg/day), L-carnitine (150 mg/kg/day) or a combination of both ginger (100 mg/kg/day) and L-carnitine (150 mg/kg/day) daily via a stomach tube for one month. All rats were sacrificed at the end of the treatment period.

E. Blood Sampling

Immediately after sacrificing, the blood from each animal was collected into a clean centrifuge tube. The blood was left to coagulate and was then centrifuged at 3000 rpm for 30 minutes to separate the serum. The separated serum was stored at -20˚C for subsequent biochemical and hormonal analyses (i.e., total antioxidant capacity [TAC], testosterone, follicle-stimulating hormone [FSH] and luteinising hormone [LH]). The circulating levels of testosterone, FSH and LH were determined using radioimmunoassay kits supplied by Lab Service Co. (Egypt) according to the method of [12]. TAC was determined according to [13].

F. Determination of the Gonadosomatic Index

The body weight of each rat was determined immediately before sacrificing. After sacrifice and dissection, the testes were removed, and individual testes were weighed to determine the gonadosomatic index:

G. Tissue Sampling for Biochemical Analysis

Immediately after weighing the genitalia, each testis was homogenised for the biochemical analysis of antioxidant enzymes, including superoxide dismutase, reduced glutathione and catalase. Superoxide dismutase activity was determined according to [14], the reduced glutathione level was determined according to the method of [15] and catalase activity was determined according to [16], [17].

H. Semen Analysis

Immediately after weighing the genitalia, one epididymis from each rat was used to assess sperm motility, count and viability according to [18].

I. Histological Examinations

Samples from the testes of the four groups were processed histologically for paraffin sections. 5-7 μm sections were prepared and stained by hematoxylin and eosin stain according to [20].

J. Statistical Analyses

The data were analysed using an analysis of variance (ANOVA) with the general linear model procedure of the SAS program [19].

III. Results

As shown in Table I, the average testis weight decreased in all experimental groups, including the ginger-treated group, L-carnitine-treated group and ginger + L-carnitine-treated group, compared with the control group; however, this decrease was not statistically significant. There was a highly significant increase ($p<0.01$) in the gonadosomatic index of all experimental groups (without significant differences between these groups) compared with the control group. In addition, the results shown in Table I indicate that the sperm counts increased in all experimental groups relative to the control group, although this increase was not statistically significant. However, there were highly significant increases ($p<0.01$) in sperm motility and viability in all treated groups (without significant differences between these groups) compared with the control group. As shown in Table II, the administration of ginger and L-carnitine, either separately or in combination, for one month increased the TAC in these groups compared with the control group; however, these differences were not statistically significant. Catalase enzyme activity increased after the administration of ginger and L-carnitine, either separately or in combination, for one month, although these differences were not statistically significant. However, after one month of treatment, there was a significant increase ($p<0.05$) in the level of reduced glutathione in the L-carnitine-treated group; to a lesser extent, the ginger-treated group and the combination group also showed significant increases (without significant differences between the two groups).

The administration of ginger, L-carnitine or a combination of ginger and L-carnitine for one month resulted in a highly significant increase ($p<0.01$) in the activity level of superoxide dismutase in these groups compared with the control group.

As shown in Table III, the levels of FSH and testosterone increased in all treated groups relative to the control group, whereas LH levels increased in the ginger-treated group and decreased in the L-carnitine-treated group and combination group compared with the control group; however, none of these differences were statistically significant. In case of male rat treated with a combination of ginger and L-carnitine daily for one month the lumen of the seminiferous tubules showed a great increase in the number of spermatozoa (Fig. 1B) compared to that observed in control group (Fig. 1A). While those treated with ginger only showed a significant increase in the luminal spermatozoa (Fig. 2A) the testis of male rat treated with L-carnitine only there was a moderate increase in the number of spermatozoa (Fig. 2B) although lower than that was observed in case of treating with ginger only.

TABLE I
EFFECTS OF GINGER, L-CARNITINE AND THEIR COMBINATION ON THE AVERAGE TESTIS WEIGHT(G), GONADOSOMATIC INDEX(%),SPERM COUNT(10^6/ML),SPERM MOTILITY(%) AND SPERM VIABILITY(%)

Parameter	Control	Ginger	L-Carnitine	Ginger + L-Carnitine
Testis weight	1.24±0.2	1.09±0.26	1.11±0.14	1.17±0.12
Gonadosomatic index	0.58±0.07 ^{B}	0.73±0.07 ^{A}	0.71±0.06 ^{A}	0.73±0.11 ^{A}
Sperm number x 10^6	34.25±18.01	57.5±14.29	56.25±15.01	59.33±24.09
Sperm motility	0.68±0.12 ^{B}	0.88±0.14 ^{A}	0.9±0.07 ^{A}	0.88±0.06 ^{A}
Sperm viability	0.78±0.08 ^{B}	0.97±0.02 ^{A}	0.97±0.02 ^{A}	0.93±0.06 ^{A}

TABLE II
EFFECTS OF GINGER< L-CARNITINE AND THEIR COMBINATION ON THE TOTAL ANTIOXIDANT (MILLIMOLES/L) CAPACITY, CATALASE ACTIVITY (U/MG) REDUCED GLUTATHIONE ACTIVITY(MG/MG PROTEIN) AND SUPEROXIDASE DISMUTASE ACTIVITY (U/MG)

Parameter	Control	Ginger	L-Carnitine	Ginger + L-Carnitine
Total antioxidant capacity	1.5±0.1	3.16±1.89	5.89±2.34	5.61±2.24
Catalase	5.39±0.6	8.2±0.73	8.8±0.47	6.29±0.59
Reduced glutathione	0.10±0.01^{b}	0.15±0.01^{ab}	0.18±0.03^{a}	0.13±0.02^{ab}
Superoxide dismutase	0.67±0.12 ^{C}	2.43±0.4 ^{A}	2±0.68 ^{AB}	1.21±0.07 ^{BC}

TABLE III
EFFECTS OF GINGER< L-CARNITINE AND THEIR COMBINATION ON MALE SEX HORMONES FSH, LH AND TESTOSTERONE)

Parameter	Control	Ginger	L-carnitine	Ginger+ L-Carntine
FSH	0.11±0.06	0.25±0.26	0.12±0.04	0.18±0.14
LH	0.14±0.03	0.16±0.07	0.12±0.02	0.13±0.02
Testosterone	0.36±0.14	1.66±0.94	0.83±0.52	1.65±0.76

Means in Tables (I,II,III) within the same row carry different capital superscripts are highly significantly ($p<0.01$) different and those carry different small superscripts are significantly ($p< 0.05$) different.

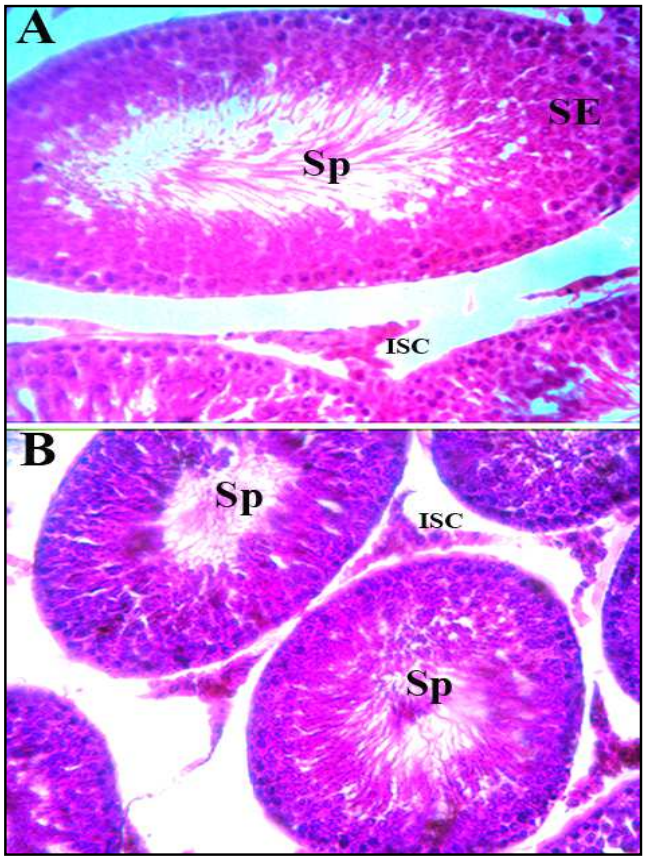

Fig. 1 represents the control group (A) the seminiferous tuules lined with seminiferous epithelium (SE) with spermatozoa (Sp) in their lumen and interstitial cells (ISC) in between them. In rat treated with a combination of ginger and L-carnitine (B) the number of spermatozoa increase greatly

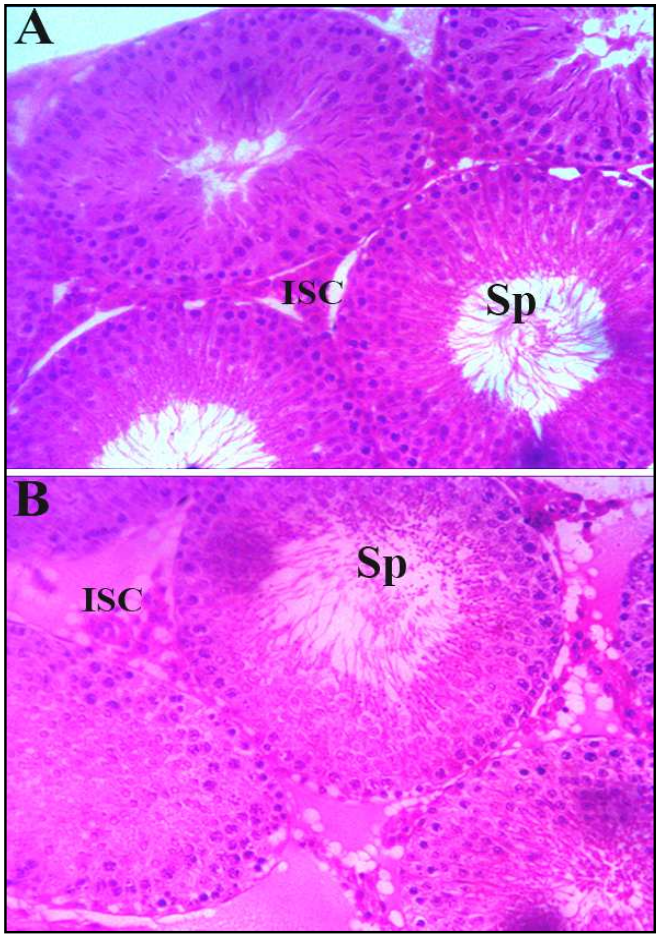

Fig. 2 represents the ginger treated group (A) the seminiferous tuules lined with seminiferous epithelium (SE) with a significant increase in the number of spermatozoa (Sp) in their lumen and interstitial cells (ISC) in between them. In rat treated with L-carnitine only (B) the number of spermatozoa increase moderately

IV. Discussion

The medicinal use of ginger dates back to ancient China and India. Ginger and its constituents have been reported to possess antiemetic, antithrombotic, antihepatotoxic, anti-inflammatory and cholagogic properties. Ginger also has antioxidative and androgenic activities. As an antioxidant, ginger has a useful effect on treating spermatogenesis disorder and poor sperm function [10].

Concerning the effect of L-carnitine on male reproduction, in several experimental and clinical studies on groups of infertile patients, the total L-carnitine level in seminal plasma was found to be low, and L-carnitine supplementation resulted in improved reproductive function [21], [22].

In our study, the daily administration of ginger, L-carnitine or a combination of both for one month decreased the average testis weight, as shown in Table I. In the ginger-treated group, the decrease in testis weight may be attributed to the antilipidemic and hypocholesterolemic effects of ginger, which results from the inhibition of cellular cholesterol synthesis with

the subsequent augmentation of LDL receptor activity and elimination of LDL from the plasma [23], [24]. In contrast, other studies have reported that ginger either had no effect on testis weight [3], [10] or led to an increase in testis weight [2], [25]. In the L-carnitine-treated group, the decrease in the average testis weight may have been due to the hypolipidemic effect of L-carnitine [26], [27]. L-carnitine was reported to increase the influx of fatty acids in the form of acylcarnitine into the mitochondria for energy production with a subsequent reduction in substrate availability for the synthesis of triglycerides in the liver. However, other studies have reported that L-carnitine had no effect on the average testis weight [27], [28].

The decreased testis weights observed in the combination group may be attributed to the synergistic effects of ginger and L-carnitine on testis weight.

In our study, as is shown in Table I, the gonadosomatic index (average testis weight relative to the body weight) increased significantly after the administration of ginger, L-carnitine or a combination of both for one month; differences between the groups were not observed. This increase may be attributed to the fact that the antilipidemic and hypocholesterolemic effects of both treatments may have been more effective in decreasing the body weights relative to the increased testis weights in these groups.

Our study showed that all treatments resulted in increased spermatozoa number, semen counts, motility and viability. In the ginger-treated group, the observed increases in sperm count, motility and viability were in agreement with other published studies [23], [24], [25]. These studies demonstrated that ginger increases these sperm parameters mainly through its antioxidant effect, which is reflected in the increased levels of antioxidant enzymes (i.e., catalase, superoxide dismutase and reduced glutathione) and the TAC, as well as through its androgenic activity, which is indicated by an increased testosterone level that promotes spermatogenic activity. However, other studies have reported that ginger administration had no effect on sperm count [10], [29].

In the L-carnitine-treated group, our results agreed with those of other studies that showed an increased in sperm parameters (sperm count, motility and viability) after the administration of L-carnitine [30], [31], [32]. These studies also reported that L-carnitine affects these sperm parameters mainly by increasing the activity of antioxidant enzymes, which is reflected in the increased levels of catalase, superoxide dismutase, reduced glutathione and TAC. These increased levels of antioxidants lead to reduced levels of free radicals available for lipid peroxidation. In contrast, other studies have reported that L-carnitine had no effect on these sperm parameters [27].

In this study, the increased sperm count, motility and viability found in the combination group, as shown in Table I and Fig. (1B), may have been due to a highly synergistic effect between ginger and L-carnitine.

[33] reported that a sophisticated antioxidant system exists in the testes, and the main role of this system involves the rapid conversion of superoxide anions to hydrogen peroxide in the presence of superoxide dismutase. This process is followed by the rapid elimination of hydrogen peroxide, mainly by glutathione peroxidase as well as catalase [34], [35], to prevent the oxidative damage of lipids, proteins and DNA. On the other hand, [36] showed that glutathione-s-transferase catalyses the conjugation of reduced glutathione's sulfhydryl group to electrophilic centres on various substances to remove them from the cell; this process aids in the detoxification of lipids and the metabolism of xenobiotics. [37] reported that catalase is of limited importance in the testes. However, there are several isoforms of glutathione peroxidase in the mitochondria, nucleus and acrosomal domain of differentiating spermatozoa that use reduced glutathione as a source of electrons to reduce hydrogen peroxide to water.

In our study, the administration of ginger, L-carnitine and a combination of both substances increased the levels of the antioxidant enzymes (i.e., catalase, reduced glutathione and superoxide dismutase) and increased the TAC, as shown in table (2).

In the ginger-treated group, these results were in accordance with other published studies [22], [38], [39] in which ginger was demonstrated to be a strong antioxidant. Its antioxidant activity has been attributed to its major active phenolic ingredients (e.g., zingerone, gingerdiol, zingibrene, gingerols and shogaols). In addition, the administration of ginger has been shown to improve oxidative stress by decreasing lipid peroxidation and protein oxidation as free radical-generating sources and elevating the levels of enzymes implicated in the antioxidant defence system.

In the L-carnitine-treated group, as shown in table (2), the increase in the level of antioxidant enzymes was in agreement with other studies [11], [40]. The antioxidant effect of L-carnitine may have been due to the role of L-carnitine in the chelation of free Fe^{+2} ions with a subsequent reduction in free radical generation [41] or its ability to enhance ATP production, which improves the overall level and activity of antioxidant enzymes in the cell [42].

The increased level of testicular antioxidant enzymes and the higher TAC in the combination group may have been caused by a synergistic effect of ginger and L-carnitine on these enzymes.

In our study, the levels of FSH and LH increased in the ginger-treated group, as shown in Table III; this result is in agreement with [39]. The primary hormonal controls on spermatogenesis involve the actions of FSH and testosterone on Sertoli cells. FSH acts on Sertoli cells by increasing the levels of cyclic adenosine monophosphate (cAMP), thus increasing protein synthesis and estradiol production [43]. However, a previous study reported that ginger administration had no effect on FSH and LH [10]. Ginger administration also increased the level of testosterone, as shown in Table III. This result corroborates previous studies in which testosterone

levels were shown to increase after the administration of ginger [24], [25], [39]. Ginger was also found to possess a strong androgenic activity, which is reflected by increased testosterone levels. [44] reported that testosterone is required for the maintenance of spermatogenesis and the inhibition of germ cell apoptosis.

In the L-carnitine-treated group, the levels of FSH and testosterone increased and the level of LH decreased. This change in testosterone levels is consistent with reports by [11] and [45] in which testosterone levels increased after L-carnitine administration. The administration of a dietary supplement containing acetyl-L-carnitine has been shown to cause an increase in testosterone levels by increasing nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) levels via enhanced acetylcholine levels. NO activates the release of luteinising hormone-releasing hormone (LHRH), which reaches the pituitary and activates the release of luteinising hormone (LH) via the activation of neural NO synthase (NOS) in the pituitary gland. When cGMP levels are elevated, it serves as an intermediate in the signalling cascade that begins with LH binding and results in testosterone production and an increase in the phosphorylation of the steroidogenic acute regulatory protein (StAR), a Leydig cell cholesterol transfer protein that provides the building blocks for testosterone synthesis. In addition, LH works with receptors located on the surface of Leydig cells to control the production and secretion of testosterone. The subsequent binding of LH to its receptor allows signalling through the cAMP pathway via guanosine triphosphate binding proteins. Signal transduction occurs through the protein kinase A pathway, which ultimately causes the release of testosterone after 30-60 minutes of LH stimulation [46]. However, a previous study reported that the inhibition of L-carnitine biosynthesis had no effect on testosterone level [47].

The administration of a combination of both ginger and L-carnitine resulted in increased levels of FSH, and this increase may have been due to a synergistic effect of ginger and L-carnitine on FSH. On the other hand, the levels of LH decreased in this group, which may have been caused by the effect of L-carnitine on LH. The increased levels of testosterone in this group may have been the result of a synergistic effect of ginger and L-carnitine on this hormone.

V. Conclusion

The daily oral administration of ginger at a dose of 100 mg/kg, L-carnitine at a dose of 150 mg/kg or a combination of both ginger and L-carnitine for one month increased sperm parameters, testicular antioxidant enzyme and testosterone hormone levels, with more pronounced positive effects in the group that received a combination of both ginger and L-carnitine. Therefore, this study suggests that the administration of a combination of ginger and L-carnitine may be beneficial for improving male sexual performance.

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