Effect of Extracts of Ginger Goots and Cinnamon Bark on Fertility of Male Diabetic Rats

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Abstract: This study was performed to investigate the effects of ginger roots and cinnamon bark extracts on fertility of male diabetic rats and levels of blood glucose as well as serum insulin and testosterone hormones. The experiment was carried out on sixty mature male Sprague Dawley rats distributed into 6 groups of 10 rats each. One group was kept as normal control, while rats of the other five groups were rendered diabetic by intraperitoneal injection of alloxan in a dose of 120 mg/kg b.wt., as a single daily dose for 3 days. Group (2) was left as diabetic control, while rats of groups (3) and (4) were given orally ginger extract at 250 and 500 mg/kg b.wt., respectively, daily for 65 days to cover the period of spermatogenesis in the rat. Rats of groups (5) and (6) were given orally cinnamon extract at the same doses of ginger and for the same period. The results showed that oral administration ginger extract at 250 and 500 mg/kg and cinnamon extract at 500 mg/kg to diabetic male rats for 65 days increased the weight of testes and seminal vesicles; improved semen quality and quantity; decreased blood glucose level and increased serum insulin and testosterone levels. The extracts also ameliorated the degenerative lesions which seen in the testes of diabetic rats. This study recommends that intake of ginger roots or cinnamon bark as a drink may be beneficial for diabetic patients who suffer from sexual impotency as their extracts induce antidiabetic activity and enhance male fertility in diabetic rats. [Journal of American Science 2010;6(10):940-947]. (ISSN: 1545-1003).

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1. Introduction:

Infertility is one of the major health problems in life, and approximately 30 % of this problem is due to male factors (Isidori *et al.*, 2006). Several factors can interfere with the process of spermatogenesis and reduce sperm quality and quantity. Some diseases and conditions such as coronary heart diseases; diabetes mellitus; chronic liver diseases; chronic smoking; insecticide contaminants; air pollutants and insufficient vitamins intake have been reported to cause deleterious effects on spermatogenesis (Mosher and Pratt, 1991). On the other hand, previous study reported that intake of antioxidants and vitamins A, B, C and E can increase stability of testicular blood barrier and protect sperm DNA from oxidative stress caused by active free radicals (Jedlinska *et al.*, 2006).

Diabetes mellitus is a chronic metabolic disease which affects millions of people all over the world. The disease is characterized by hyperglycemia due to insulin deficiency or insulin resistance. Hyperglycemia occurs when the liver and skeletal muscles can not store glycogen and/or the cells become unable to utilize glucose. The prevalent treatment of diabetes mellitus besides controlling food intake; treating obesity; proper exercise and changing life style includes administration of oral hypoglycemic drugs and subcutaneous injection of insulin (Rang and Dale, 1991).

Several medicinal plants were examined for their hypoglycemic and antidiabetic activities and some of them have been selected to develop new drug sources to be safety used for treating diabetes mellitus (Eskander and Jun, 1995). Some of these plants decreased the blood glucose level in experimental animals such as *Zizyphus spina christi* (Glombitza *et al.*, 1994); Fenugreek (Al Habori and Abdel Rhaman, 1998); *Urtica dioica* (Bijan-Farzamie *et al.*, 2003); and *Balanites aegyptiaca* (Shalaby and Khater, 2007). Other plants increased the level of insulin in man, rats and mice such as *Rhazya stricta* (Ali, 1997); *Viscum album* (Gray and Flatt, 1999) and *Urtica dioica* (Bijan-Farzamie *et al*., 2003).

Ginger (*Zingiber officinale* L., Family *Zingiberaceae*) roots are commonly used as culinary spice and medicinally used for its antioxidant (Sekiwa *et al.*, 2000), androgenic (Kamtchouing *et al.*, 2002) and hypoglycemic (AL-Amin *et al*., 2006) activities which were reported in animal models. The active ingredients of ginger roots and leaves such as zingerone, gingerdiol, zingibrene, gingerols and shogaols produced antioxidant activity (Zancan *et al.*, 2002). The natural antioxidants can protect DNA and other molecules from cell damage induced by oxidation and can improve sperm quality and increase reproductive efficiency of men (Yang *et al.*, 2006). Ginger was also found to possess a protective effect against DNA damage induced by H_2O_2 and enhanced sperm healthy parameters in rats (Khaki *et al.*, (2009).

Cinnamon (*C. zeylanicum*, Family *Lauraceae*) bark is commonly used in Arabian countries as a spice for most foods. In Eastern and Western folk medicine it used for treating abdominal and chest pains, chronic diarrhea, hypertension, kidney disorders and rheumatism. Intake of 3g or 6g of cinnamon bark reduced serum glucose in people with type 2 diabetes (Khan *et al.*, 2003). Cinnamon extracts have also demonstrated hepatoprotective and antioxidant effects in CCL4 - intoxicated rats (Moselhy and Ali, 2009).

The present study was designed to investigate the effects of ginger roots and cinnamon bark extracts on male fertility in diabetic rats and levels of blood glucose as well as serum insulin and testosterone hormones.

2. Materials and Methods:

2.1 Plants:

Ginger (*Zingiber officinale* L., Family *Zingiberaceae*) dried roots and cinnamon (C. *zeylanicum*, Family *Lauraceae*) dried bark were obtained from local market of Herbs and Medicinal plants, Cairo, Egypt. Authentication of both plants was carried out by staff members of Botany Department, Faculty of Science, Cairo University, Egypt.

2.2 Rats:

Sixty mature male albino rats each weighing 180-190 gm b.wt. and 14-16 weeks old of Sprague Dawley strain were obtained from the Laboratory Animal Colony, Helwan, Egypt. Rats were kept under hygienic conditions in plastic cages, fed on basal diet and water was provided ad libitum.

2.3 Alloxan:

It was purchased from El-Gomhoryia Company for Chemicals; Cairo, Egypt in the form of white powder packed in tightly closed bottles each containing 25gm alloxan monohydrate.

2.4 Biochemical kits:

Glucose enzymatic kits of BioMeriuex were purchased from Alkan Company for Chemicals and Biodiagnostics, Dokki, Egypt for determination of serum glucose level. Radioimmunoassay kits were obtained from Gamma Trade Company, Egypt for estimating of the levels of serum insulin and testosterone hormones in treated rats.

2.5 Preparation of basal diet:

Basal diet was prepared according to Reeves et al. (1993). It was consisted of 20 % protein (casein), 10% sucrose, 4.7% corn oil, 2% choline chloride, 1% vitamin mixture, 3.5 % salt mixture and 5% fibers (cellulose). The remainder was corn starch.

2.6 Preparation of plant extract:

The method of plant extraction was described by Shalaby and Hamowieh (2010). In this method, the dried powder of ginger or cinnamon (500 gm from each plant) was soaked in 2 liter of 90% ethyl alcohol overnight and extracted till complete exhaustion by percolation several times with ethanol as a solvent. The solvent was evaporated by using Rotavapour apparatus (made in Russia) connected to a vacuum pump and the temperature was adjusted to 50ċ till yielding a semisolid ethanolic extract. Known grams of the obtained extract were dissolved in few drops of Tween 80 as a suspending agent, and then distilled water was added to prepare a solution of desired concentration.

2.7 Experiment and Grouping of rats:

The rats were divided into 6 groups of 10 animals each. The 1st group was fed on the basal diet and served as normal control, while the other five groups were given alloxan by intraperitoneal injection of a single daily dose of 120 mg/Kg b.wt. for 3 days to induce moderate stable diabetes as described by Ashok et al. (2007). The 2nd group of rats was left as diabetic control, while diabetic rats of the 3rd and 4th groups were given orally ginger extract at 250 and 500 mg/kg b.wt., respectively, for 65 days to cover the period of spermatogenesis in the rat.The 5th and 6th groups of diabetic rats were given orally cinnamon extract at the same doses of ginger and for the same period. At the end of experiment period, blood samples were taken for separation of serum which was used for estimating the levels of blood glucose and insulin and testosterone hormones. Rats were anaesthetized and epididymal contents were taken from the tail of epididymis for semen analysis. The rats were then sacrificed and the testes, seminal vesicle and prostate gland were dissected out and weighed. The testes were preserved in 10% neutral formalin solution till processed for histopathological examination.

2.8 Blood sampling and biochemical analyses:

Blood samples were collected from the orbital plexus of veins by capillary microtube and left to clot for separating the serum after centrifugation at 3000 rpm for 15 minutes. Serum samples were directly frozen at –10 Ċ till biochemical analyses. Estimation of blood glucose was carried out using enzymatic glucose kits according to the method described by Siest et al. (1981). Serum insulin was determined using radioimmunoassay method as described by Yallow and Bauman (1983). Serum testosterone concentration was determined according

to the method of Wilke and Utley (1987) using gamma counter apparatus (made in West Germany).

2.9 Semen analysis:

Epididymal contents of the treated rats were obtained after cutting the tail of epididymis, squeezing it gently on clean slide and the sperm progressive motility and cell count were determined according to the method described by Bearden and Fluquary (1980). Microscopic examinations of the seminal smears stained with Eosin Nigrosin stain were carried out to determine the percentages of sperm viability (ratio of alive/dead) and sperm cell abnormality according to Amman (1982).

2.10 Histopathological examination:

Testes of the treated rats were taken and fixed in 10 % neutral formalin solution. The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol. These specimens were cleared in xylene, embedded in paraffin, sectioned at 4-6 microns thickness and stained with Hematoxylen and Eosin (H &E) then examined microscopically according to the method described by Luna (1968).

2.11 Statistical analysis:

Data were expressed as means ± S.E. and statistical analysis was carried using computerized SPSS program. Significance was performed using the least significant difference and paired Student "t" test according to Snedecor and Cochran (1986).

3. Results:

Interaperiotenal administration of alloxan to normal rats in a dose of 120 mg/kg b.wt. caused significant ($P < 0.01$) decreases in the weight of testes, seminal vesicle and prostate glands. Oral administration of ginger extract at 250 and 500 mg/kg b.wt. to diabetic rats for 65 days significantly increased the weight of testes and seminal vesicle and did not affect the weight of prostate glands as compared to the diabetic control group. Cinnamon extract when given to diabetic rats by the same doses and for the same period did not significantly affect the weight of the above mentioned sexual organs as shown in Table (1).

Concerning semen picture, it was found that alloxan decreased the sperm progressive motility, sperm count and viability, but increased the percentage of sperm cell abnormality in diabetic rats as recorded in Table (2). The most frequently seen sperm cell abnormalities in the seminal smears of diabetic rats were detached head and coiled tails as demonstrated in Fig. (1A and B). Oral administration of either ginger or cinnamon extract at 250 and 500 mg/kg b.wt. for 65 days to diabetic rats induced significant ($P < 0.001$) increases the sperm progressive motility, sperm count and viability as well as decreases in the percentage of sperm cell abnormality.

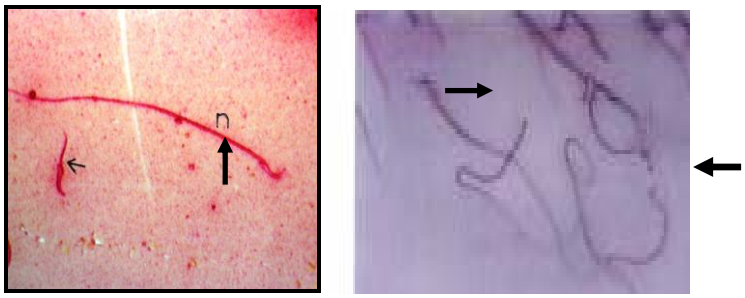
As shown in Table (3), the serum glucose and insulin hormone levels of diabetic rats were 225.5 ± 4.6 mg/dL and 3.66±1.2 µU/ml versus 95.8 ± 3.5 mg/dL and 6.40±1.5 µU/ml of normal rats, respectively. Oral administration of ginger extract at 250 and 500 mg/kg b.wt. for 65 days to diabetic rats significantly ($P < 0.01$) decreased serum glucose concentration and increased insulin level as compared to the diabetic control group. Cinnamon extract when given to diabetic rats at the same doses and for the same period significantly ($P < 0.05$) reduced serum glucose level, but did not affect the level of insulin hormone as compared to the diabetic control group.

Table (1): Effect of oral administration of extracts of ginger and cinnamon for 65 days on the weight of sexual organs of male diabetic rats. (n= 10 animals)

Groups and Treatment	Mean ± SE of sexual organs weight (g)		
	Testes	Seminal vesicles	Prostate glands
Normal control Distilled water (1 ml)	2.80 ±0.22	1.75 ± 0.15	0.66 ± 0.01
Diabetic control Alloxan (120 mg/kg)	1.65** ±0.12	1.00** ± 0.14	0.23** ± 0.01
Ginger extract (250 mg/kg)	2.15** ±0.33	1.51* ± 0.16	0.35 ± 0.03
Ginger extract (500 mg/kg)	2.40** ±0.26	1.65* ± 0.18	0.39 ± 0.02
Cinnamon ext. (250 mg/kg)	1.65 ±0.13	0.87 ± 0.15	0.22 ± 0.04
Cinnamon ext. (500 mg/kg)	1.90 ±0.22	1.12 ± 0.12	0.33 ± 0.01

The treated groups were compared to the diabetic control group using Student 't' test

* Significant at $P < 0.05$ ** Significant at $P < 0.01$



(A) (B)

Fig (1): Seminal smear obtained from a diabetic control rat given alloxan showing detached head (A) and coiled tails (B). (Eosin Nigrosin stain X 60).

Table (2): Effect of oral administration of extracts of ginger and cinnamon for 65 days on sperm cell characteristics of male diabetic rats. (n= 10 animals)

Groups and Treatments	Sperm cell characteristics (Mean ± S.E.)			
	Motility (%)	Count (10^6/ epididymis)	Viability (%)	Abnormality (%)
Normal control Distilled water (1ml)	90.00 ± 1.0	77.67 ± 0.48	89.0 ± 0.12	3.67 ± 0.18
Diabetic control Alloxan (120 mg/kg)	50.00*** ± 1.03	55.00*** ± 0.33	60.0*** ± 0.16	8.25 ± 0.08
Ginger extract (250 mg/kg)	64.00*** ± 2.30	64.67*** ± 0.43	65.0*** ± 0.10	4.33 ± 0.18
Ginger extract (500 mg/kg)	85.0*** ± 0.22	72.67*** ± 0.28	75.0*** ± 0.13	3.76 ± 0.18
Cinnamon ext. (250 mg/kg)	60.00*** ± 0.12	58.00*** ± 0.35	66.0*** ± 0.15	5.43 ± 0.18
Cinnamon ext. (500 mg/kg)	65.00*** ± 0.20	59.00*** ± 0.30	72.0*** ± 0.13	4.24 ± 0.24

The treated groups were compared to the diabetic control group using Student 't' test
*** Significant at P < 0.001

Table (3): Effect of oral administration of extracts of ginger and cinnamon for 65days on blood glucose and insulin hormone levels in male diabetic rats. (n= 10 rats)

Groups and Treatments	Glucose level (mg/dL)	Insulin level (µU/ml)
Normal control Distilled water (1 ml)	95.80 ± 3.5	6.40 ± 1.5
Diabetic control Alloxan (120 mg/kg)	225.50** ± 4.6	3.66** ± 1.2
Ginger extract (250 mg/kg)	212.97** ± 5.9	4.90* ± 1.4
Ginger extract (500 mg/kg)	195.90** ± 6.2	5.10** ± 1.2
Cinnamon ext. (250 mg/kg)	216.22* ± 7.3	4.00 ± 1.4
Cinnamon ext. (500 mg/kg)	218.50 * ± 8.5	4.10 ± 1.3

The treated groups were compared to the diabetic control group using Student 't' test * Significant at P < 0. 05 ** Significant at P < 0. 01

Data in Table (4) show that intraperitoneal administration of alloxan to normal rats at a dose of 120 mg/kg b.wt. induced a significant (P < 0. 01) decrease in serum testosterone hormone to 3.3 ± 0.13 ng/dL versus to 7.7 ± 0.14 ng/dL in the normal control rats. Oral administration of either ginger or cinnamon extract at 25o and 500 mg/kg for 65 days to diabetic rats caused significant (P < 0. 01) increases in serum testosterone levels as compared to the diabetic control rats.

Histopathological examination of the testes of normal rats showed normal histological structure of active mature functioning seminiferous tubules associated with complete spermatogenic series as demonstrated in Fig. (2). The testes of alloxan – induced diabetic rats revealed marked degeneration of most seminiferous tubules with absence of spermatogenic series in tubular lumen as shown in

Fig.(3). Microscopic examination of the testes of rats given ginger extract at 250 and 500 mg/kg b.wt. revealed normal histological structure of most seminiferous tubules with normal spermatogenic series as illustrated in Fig (4) and Fig.(5). The testes of rats given orally cinnamon extract at 250 mg/kg b.wt. showed mild degeneration of most seminiferous tubules associated with normal spermatogenic series as demonstrated in Fig (6). Examination of the testes of rats given cinnamon extract at 500 mg/kg b.wt. revealed showing normal histological structure of most seminiferous tubules with normal spermatogenic series as shown in Fig. (7).

Table (4): Effect of oral administration of extracts of ginger and cinnamon for 65 days on serum testosterone hormone in male diabetic rats. (n= 10 rats)

Groups and Treatments	Testosterone level (ng/dL)
Normal control Distilled water (1 ml)	7.73 ± 0.14
Diabetic control Alloxan (120 mg/kg)	3.30** ± 0.13
Ginger extract (250 mg/kg)	5.18** ± 0.11
Ginger extract (500 mg/kg)	6.46** ± 0.14
Cinnamon ext. (250 mg/kg)	5.46** ± 0.13
Cinnamon ext. (500 mg/kg)	5.64** ± 0.15

The treated groups were compared to the diabetic control group using Student 't' test

** Significant at P < 0. 01

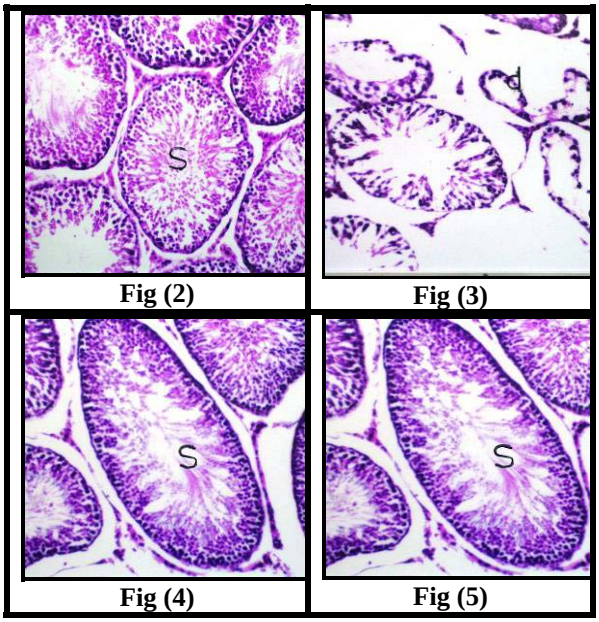


Fig (2) Fig (3)

Fig (4) Fig (5)

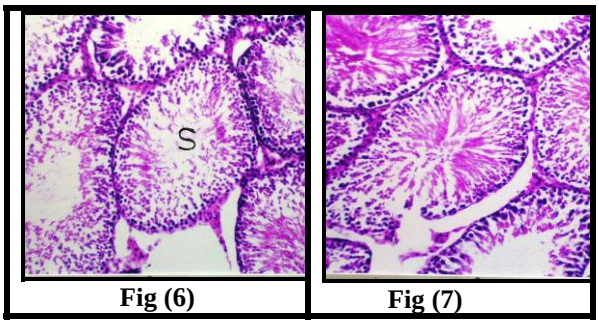


Fig (6) Fig (7)

Fig. (2): Testis of a control rat showing normal histological structure of active mature functioning seminiferous tubules(S) associated with complete spermatogenic series.

Fig. (3): Testis of a diabetic rat showing marked degeneration (d) of most seminiferous tubules with absence of spermatogenic series in tubular lumen.

Fig. (4): Testis of a rat given of ginger extract at 250 mg/kg b.wt. for 65 days showing normal histological structure of most seminiferous tubules with normal spermatogenic series.

Fig. (5): Testis of a rat given ginger extract at 500 mg/kg b.wt. for 65 days showing normal histological structure of most seminiferous tubules with normal spermatogenic series.

Fig. (6): Testis of a rat given cinnamon extract at 250 mg/kg b.wt. for 65 days showing mild degeneration of most seminiferous tubules with normal spermatogenic series.

Fig. (7): Testis of a rat given cinnamon extract at 500 mg/kg b.wt. for 65 days showing normal histological structure of most seminiferous tubules with normal spermatogenic series. (H & EX 40)

4. Discussion:

The current study was carried out to determine the effect of extracts of ginger roots and cinnamon bark on fertility of male diabetic rats following oral administration for 65 days (period of spermatogenesis in the rat). In addition, their effects on the levels of blood glucose and insulin and testosterone hormones were also estimated.

The obtained results revealed that intraperitoneal administration of alloxan to normal male rats in a dose of 120 mg/kg b.wt. for 3 days decreased the weight of testes, seminal vesicle and prostate glands, induced marked testicular degeneration, lowered semen quality and quantity, increased blood glucose and decreased serum insulin and testosterone levels. It is well known that diabetes is positively associated with lowered male fertility and sexual dysfunction (Mosher and Pratt, 1991). Recently, Sandra *et al.* (2008) concluded that the neuropathy and vascular insufficiency which caused by diabetes may be related to sexual dysfunction

Concerning ginger extract, the obtained results showed that its oral administration at 250 and 500 mg/kg for 65 days to male diabetic rats caused increases in the weight of testes and seminal vesicle, a decrease in blood glucose associated with increases in serum insulin and testosterone levels and an improvement of sperm motility and quantity as well as alleviation testicular degenerative changes that seen in the testis of diabetic rats. These findings agree with those reported by Morakino *et al.* (2008) and Khaki *et al.* (2009) who concluded that ginger may be promising in enhancing sperm healthy parameters. The authors attributed the improvement of reproductive functions of male rats by ginger to its antioxidant and androgenic activities. The alleviation of testicular lesions seem in diabetic rats after oral administration alcoholic extract of ginger, that reported in this study, may be explained by the previously reported antioxidant and androgenic effects of ginger and/or by its antidiabetic activity. The reported antidiabetic activity of ginger that evident by hypoglycemia and hyperinsulinemia by large dose of ginger, in this study, was similar to that those obtained by Akhani *et al.* (2004), Kadnur and Goyal (2005), Ojewole (2006) and Nammi *et al.* (2009). The authors concluded that the ethanolic extract of ginger roots produces an antidiabetic effect and increases insulin secretion in streptozotocin-induced diabetic rats. The improvement of male reproductive function by ginger reported in this study could be explained by its direct cytoprotective activity on testicular tissue that seem by histopathological examination or indirectly via increasing serum testosterone or lowering serum glucose and increasing serum insulin levels.

With regard to cinnamon extract, the present data revealed that its oral administration at the large dose (500 mg/kg b.wt.) decreased blood glucose level associated with increases in serum insulin and testosterone levels and an improvement of sperm motility and quantity as well as alleviation of testicular degenerative changes that seen in the testis of diabetic rats. These findings are partially similar to those reported by Khan *et al.* (2003) who concluded that intake of 3 gram or 6 gram of cinnamon reduces the fasting serum glucose in people with type 2diabetes. The hypoglycemic effect cinnamon extract which reported her it may be due to its hyperinsulinemia that evident in this study. The improvement in fertility parameters that caused by large dose of cinnamon extract could be attributed to its antioxidant activity that previously reported by Moselhy and Ali (2009). The authors concluded that cinnamon extracts have an antioxidant effect in CCL4 - intoxicated rats. Yang *et al.* (2006) concluded that the natural antioxidants can protect DNA and other molecules from cell damage induced by oxidation and can improve sperm quality and increase reproductive efficiency of men. Jedlinska *et al.* (2006) reported that intake of antioxidants and vitamins A, B, C, and E can increase stability of testicular blood barrier and protect sperm DNA from oxidative stress caused by active free radicals. In addition, the enhancement of fertility properties which produced by cinnamon extract could be explained by its direct effect on the testes causing an increase in testosterone secretion which reported in this study.

In conclusion, the oral administration ginger extract at 250 and 500 mg/kg or cinnamon extract at 500 mg/kg to diabetic male rats for 65 days increased the weight of testes and seminal vesicles, improved semen quality and quantity; reduced blood glucose level and increased serum insulin and testosterone levels. It also alleviated the degenerative lesions which seen in the testes of diabetic rats. Therefore, this study recommends that intake of ginger roots or cinnamon bark as a drink may be useful for diabetic patients who suffer from sexual impotency as their extracts produce antidiabetic activity and exhibit fertility enhancing properties in male diabetic rats.

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