

Beneficial Effects of Hydro-alcoholic Extract of Ginger Rhizome on Deleterious Effects Produced by Cimetidine on Sertoli Cells and Leydig Cells Functions in Male Mice

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Abstract

Background: Cimetidine, a common antpeptic ulcer agent, is well known to be associated with deleterious effects on male reproductive parameters. Ginger rhizome (*Zingiber officinale*) has been reported to counteract the H₂-receptor antagonistic activity of cimetidine.

Objectives: The aim of this study is to investigate the role of hydro-alcoholic extract of ginger rhizome on some reproductive parameters and its interaction with cimetidine in male mice.

Materials and Methods: The parameters measured were: the number of sertoli cells and leydig cells (by standard histopathological techniques) and serum testosterone (by radio immune assay). Forty adult male mice divided into four equal groups (10 mice for each); the 1st group was left as control, the 2nd group was given hydro-alcoholic extract of ginger rhizome, the 3rd group was given cimetidine, the 4th group was administrated hydro-alcoholic extract of ginger rhizome orally at a dose of distilled water, 60,35, 60 and after 15 minutes followed by cimetidine at a dose of 35mg/kg B.W respectively once a day for 38 days of experiment (one spermatogenesis period). Hydro-alcoholic extract of ginger rhizome was prepared by Soxhlet apparatus technique.

Results: Treatments with cimetidine alone showed a significant decrease, while with ginger extract alone showed a significant increase in all parameters when compared with the control group (P<0.05). While the combination treatment of cimetidine with ginger showed similar results to that of the control group (P>0.05).

Conclusion: Hydro-alcoholic extract of ginger could improve the efficiency the reproductive parameters of male mice, and alleviate the possible side effects of cimetidine.

Keywords: *Zingiber officinale* rhizome, Cimetidine, male reproductive system.

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Introduction

Ginger (*Zingiber officinale*, *Z. officinale*) has been used as a medicine since ancient time ⁽¹⁾. In Asian medical practices, dried ginger has been used to treat dyspepsia, diarrhea and nausea ⁽²⁻⁵⁾. Both antioxidative ⁽⁶⁾ and androgenic activity of *Z. officinale* were reported in animal models ⁽⁷⁾. This activity is reflected by the increase of both testis weight and serum testosterone level, of the major active ingredients of *Z. officinale* such as Zingerone, Gingirdiol, Zingibrene, and particularly Gingerol and Shagol, have antioxidant activity ⁽⁸⁾. In addition to antioxidant, it also has analgesic and antipyretic properties ^(9, 10, and 11). Cardiovascular actions of *Z. officinale* such as decrease in blood pressure, heart rate ⁽⁸⁾ and blood glucose ⁽¹²⁾ are well known. These two active compounds have been found to be responsible for the analgesic, anti-emetic, antipyretic and suppression of prostaglandin synthesis of *Z. officinale* ⁽¹³⁾. Ginger may also produce its antitumor effect by inducing apoptosis, in cancer cell ⁽¹⁴⁾. Ginger may antagonize the activity of proton pump inhibitors and H₂ blockers by means of increased production of gastric acid ⁽¹⁵⁾. Cimetidine is a potent competitive H₂ receptor blocker; it is extensively used for peptic ulcers ⁽¹⁶⁾. Cimetidine is a prophylactic drug for colorectal cancer, in addition treatment of Zollinger–Ellison syndrome, heart burn, oesophagitis, upper gastrointestinal bleeding and paracetamol overdose ⁽¹⁷⁾. Sexual dysfunction has been recognized as adverse reaction after cimetidine treatment ⁽¹⁸⁾. This study was conducted to determine the role of hydro alcoholic extract of ginger rhizome on some reproductive parameters and study the deleterious effect of cimetidine.

Materials and Methods

Ginger was purchased from the local market (Baghdad) and certified at the Iraqi National Herbarium in Abu Graib, in 15/3/2007, letter No.300. The ginger herb was cleaned and grinded by electrical blender. The hydro-alcoholic extract of ginger was prepared by use of ethanolic alcohol (70% concentration) according to the method of (19) by the use of Soxhlet apparatus technique. After that, the extract was concentrated by use the rotary evaporator. The dry extract was placed in incubator under 38-40°C for complete dryness of the sample. The final extract was kept frozen at -20°C until use.

Forty male mice were randomly divided into 4 groups, (10 animals per group) and handled as follows: 1st group was given distilled water reserved as control group; 2nd group was given hydro-alcoholic extract of ginger rhizome, (60 mg/kg B.W.) (20, 21), 3rd group was given cimetidine (35 mg/Kg B.W.) ⁽²²⁾, and finally 4th group was given ginger (60 mg/kg B.W.) and after 15 minutes followed by cimetidine (35 mg/Kg B.W.). All groups were orally administered daily doses for 38 days (One spermatogenesis period).

After the end of treatment, animals were sacrificed and abdominal incision was done, blood samples were taken via cardiac puncture. Testis excised and preserved in formalin 10%. Histological sections were prepared according to (23) for histological study. The leydig cells were calculated and evaluated as follows: (24) The mean number of leydig cells per seminiferous tubule. The sertoli cells were calculated as follows: The mean number of sertoli cells per seminiferous tubule was obtained by dividing the total number of sertoli cells in the entire histological section by the total number of seminiferous tubules. Levels of serum testosterone hormone were measured by Radio-immunoassay (RIA) kit.

Results

Sertoli and leydig cells number

The numbers of sertoli and leydig cells in ginger treated group, each of which, showed significant increase ($P<0.05$) compared with the control group while in the cimetidine treated group decreased significantly ($p<0.05$) compared with that of the control group; while in animals treated with combination of ginger and cimetidine sertoli and leydig cells numbers did not differ significantly ($P>0.05$) from those of control group (Table- 1).

Serum testosterone

Serum testosterone level in ginger treated group showed significantly increased ($P<0.05$) compared with that of the control group but in cimetidine treated group showed significant decrease ($P<0.05$) compared with the control group; while in ginger plus cimetidine treated group no significant difference ($P>0.05$) was observed compared with the control group (Table -1).

Table (1): **Effect of ginger, cimetidine and ginger + cimetidine on sertoli cell, leydig cells and serum testosterone level.**

Parameters Groups	Sertoli Cell	Leydig Cell	Serum Testosterone level (ng/ml)
Control	13.50±1.050 B	11.60±0.88 B	0.90±0.17 A
Ginger 60mg/kg B.W	18.10±0.88 A	15.40±0.69 A	2.59±0.30 B
Cimetidine 35mg/kg B.W	9.10±0.97 C	7.40±0.60 C	0.15±0.020 c
Ginger+Cimetidine 60+35mg/kg B.W	14.80±1.20 B	12.80±1.37 AB	0.67±0.30 AB
LSD	2.923	2.7344	0.6548

Mean ± standard error of mean, (n=5).

Discussion

The number of sertoli cells decreased after cimetidine treatment, this may be directly attributed to the decrease in androgen levels ⁽²⁵⁾. However, It has been suggested that cimetidine may impair peritubular cells secretion, that is essential for development and maintenance of sertoli cells function, and thus in turn cimetidine may cause sertoli cells degeneration (atrophy) ^(26, 27). Further, another argument has been put forward ^(26, 28) that cimetidine may produce its antifertility effect via its antiandrogenic activity by somehow interacting with the hypothalamic-pituitary-leydig cell axis resulting in reduced FSH. On the other hand, the significant increase in sertoli cells number per seminiferous tubules in ginger treated group suggest a promoting effect on sertoli cells division process, probably by interacting with FSH contributing in spermatogenesis via increasing spermatogonia and sertoli cell ⁽²⁹⁾. While others ⁽⁷⁾ proposed that this effect of ginger extract may be due to enhanced alpha-glycosidase activity in epididymus and thus more fructose in seminal vesicle and this in turn leads to increased androgen synthesis. The major active ingredients in *Z. officinale* (Zingerone, Gingerdiol, Zingibrene, Gingerols and Shogaols) have antioxidant activity ^(6,8).

Its concluded that hydro-alcoholic extract of ginger produced effect that counteract the deleterious effect on reproductive parameter produce by cimetidine and there for combination use ginger with cimetidine may play a beneficial therapeutic role.

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