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Study of Clomipramine effects on pituitary-gonadal axis on adult laboratory male rats

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Abstract
The incidence of obsessive-compulsive and depression disorders increases prescription serotonin reuptake medicines and taking these medicines have several side effects on reproductive system, especially on sexual hormones in male. Nowadays, the approach for reducing side effects of chemical drugs is medicinal plants usage. So, the purpose of the study is investigation on antioxidant effects of ginger rhizome extract for reducing of Clomipramine effects on testosterone, LH and FSH hormones. 42 adult male rats were divided into control, sham, and experimental groups. Experimental group 1 only received Clomipramine and experimental groups 2, 3, and 4 received rhizome extract with Clomipramine. At the end of 21 days blood samples were collected and Radioimmunoassay method was used to measure serum levels of LH, FSH and testosterone hormones. It is found that Clomipramine medicine has damaging effect on sexual hormones and ginger extract improves secretion of these hormones due to its antioxidant properties.

Keywords: ginger, Clomipramine, LH, FSH, Testosterone, Laboratory Rats

1. Introduction
Today, with increased frequency of depression among communities, consumption of antidepressants such as Clomipramine has become very common. The problem is that many people who use these medicines may be in childbearing age. Peripheral and central mechanism including some mediators such as serotonin, dopamine, and noradrenaline plays a great role in sexual behaviors [1-3]. Studies have shown that separate inhibitors of serotonin reuptake are the most effective medicine available to treat obsessive-compulsive disorders [4]. Clomipramine (by brand name of Anafranil) is one of tri-cyclic medicine which derived from dibenzopyridine. This medicine is anti-obsession and anti-depressant and is used to treat these disorders [5]. Studies have shown that Clomipramine has more effects on inhibition of serotonin reuptake and blocking of dopamine receptors compared to other tri-cyclic antidepressants [6]. This action increases prolactin release and inability to reach orgasm through HT2-5 mediators [7, 8]. Recent studies have shown that dopamine and serotonin inhibitors severely influence on steroid hormones. Also studies have found that antidepressants have harmful effects on sexual function and create erectile dysfunction [10] as well as reduction of total cholesterol levels that is a precursor of testicular androgens production in Leydig cells [11]. So, peoples who consume antidepressants are in search for use of antioxidants to reduce the effects of this medicine.
Today, due to economical and therapeutic importance of medicinal plants and their innocuousness and development of herbal therapy attitude in the world, estimation of effective yield of these plants have particular importance [12]. The application of medicinal plants has long been common among people in Iran and other countries and in the recent years a comprehensive approach to use of medicines with natural and in particular herbal origin is created among people [13]. Ginger is a medicinal plant that serves by public. In performed studies on chemical compositions of ginger rhizome have shown that this plant contains large amounts of antioxidant ingredients, such as flavonoids, glutathione and many vitamins [14, 15]. Studies have shown that available ingredients in ginger can cause restoration of DNA molecules. It is also stated that antioxidant compounds available in the extract eliminate free radicals and active metabolites from body. So, they can have beneficial effects on reproductive systems [16-18]. With respect to the issues mentioned above, the purpose of the study is investigation on ginger extract effects on hormone-pituitary-gonadal axis in Clomipramine treated-male rats.

2. Materials and Methods

The study was performed from March 2014 to September 2014. All ethical use of laboratory animals has been respected in this study according to Shiraz University Animal Welfare Committee guidelines. A number of 42 adult male Wistar rats which were prepared from Razi Serum center in Shiraz, Iran, were used in the study. All animals were kept at 22±2 ˚C with free access to food and water and at standard condition of 12 hours of light and 12 hours of darkness. In order to make adaptation to environment, the entire tests were performed 2 weeks after establishment of the rats. The animals were grouped as follows: ±

1- Control group: the rats in the group were kept in normal conditions, without receiving of any drug.
2- The sham group: the rats received distilled water as a solvent of the drug and they orally received the extract.
3- The experimental group 1: the rats were orally received 10 mg/kg of Clomipramine.
4- The experimental group 2: the rats were orally received 10 mg/kg of Clomipramine with 50 mg/kg of ginger extract.
5- The experimental group 3: the rats were orally received 10 mg/kg of Clomipramine with 100 mg/kg of ginger extract.
6- The experimental group 4: the rats were orally received 10 mg/kg of Clomipramine with 200 mg/kg of ginger extract.

2.1 Ginger Extract and Clomipramine Preparation Methods

Ginger rhizomes were powdered first and percolation method was used for extraction. Then, the dried powdered was poured in cylindrical portion of percolator device, which was filled up to two-third with alcohol (80%) and the rest with water. The valves of device were closed, when the first solution had been exited from the last valve and after passing of 24 hours, they opened and the extract collected. Then it was dried at a temperature of 40-30 ˚C under a microbe-free environment.

Clomipramine drug as 10 mg tablets were obtained from a pharmacy in Shiraz, Iran.

Rats treated orally for a period of 21-day. At the end of the experiment, they anesthetized with diethyl ether and then blood samples were taken from them and collected into some sterile plastic tubes. They were coagulated at room temperature for 20 minutes and the samples were then centrifuged for 15 minutes at speed of 3000 rpm, their serum isolated and were kept at -20 ˚C to measure the activity of LH, FSH and testosterone hormones. The mentioned hormones were measured by radioimmunoassay method. The results were analyzed using SPSS software version 18 and one-way analysis of variance (one-way ANOVA) and Duncan's tests ($p \leq 0.001$).

3. Results

Results show that changes of LH hormone increased in the experimental group 1 which received Clomipramine compared to the control and it was not significant at ($p \leq 0.001$). LH hormone concentration in the experimental groups 3 and 4 had significant reduction at ($p \leq 0.001$) compared to control and the experimental group 1. (Chart 1)

According to Diagram 2, the concentration of FSH in the other experimental groups did not have a significant change at ($p \leq 0.001$) compared to control.

According to Diagram 3, the concentration of testosterone hormone in the experimental group 1 had significant reduction at ($p \leq 0.001$) compared to control. And the concentration of testosterone hormone in the experimental groups 2, 3 and 4 had significant increase compared to the experimental group 1.

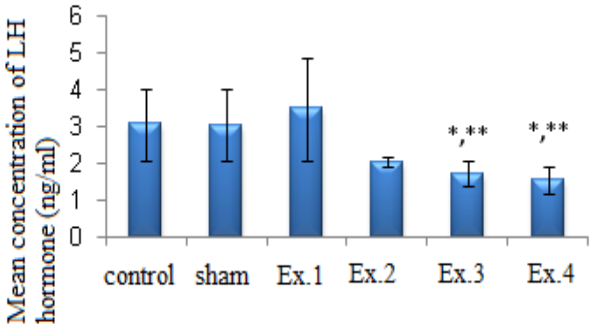

Chart 1: changes related to concentration of LH hormone in the experimental groups

Points have shown as S.E±Mean. * represents significant reduction compared to control and the experimental group 1.

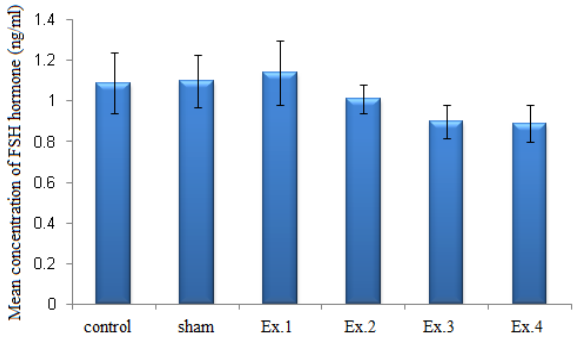

Chart 2: changes related to concentration of FSH hormone in the various groups

Points have shown as S.E±Mean. There is a significant difference at ($p \leq 0.001$) compared to the control group.

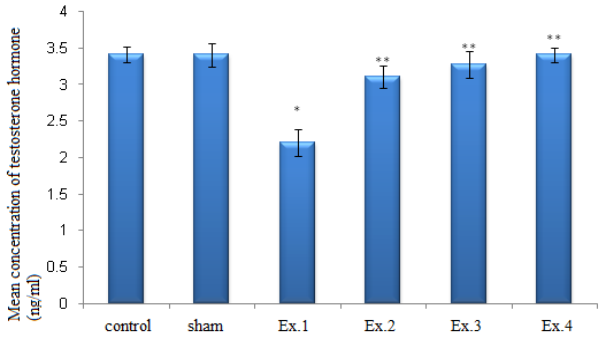

Chart 3: changes related to concentration of testosterone hormone in various groups

Points have shown as S.E±Mean. * Represents a significant difference at ($p \leq 0.001$) compared to the control group and * represents a significant difference at ($p \leq 0.001$) of other groups compared to the experimental group 1.

4. Discussion

In the present study, increase of LH, FSH and testosterone hormones was observed in Clomipramine groups, and the increase was not statistically significant. The concentration of testosterone hormone in the experimental group 1 had a significant reduction compared to control.

Increase of testosterone hormone under normal condition by effecting on hypothalamus and anterior pituitary helps initiate

negative feedback mechanism and as a result reduces gonadotropin hormones [19, 20]. In studies showed that serotonin reuptake inhibitors (e.g., Clomipramine) by reducing of LH receptors in Leydig cells reduce testis activity to secrete testosterone [11]. Also, taking of serotonin reuptake inhibitors reduces the amount of total cholesterol that is a precursor of testicular androgens production in Leydig cells [11]. As a result, the inhibitory effect of androgens on androgenic receptors through reduction of LH receptors leads to negative feedback mechanism, so the concentration of LH increases. A study found that serotonin reuptake inhibitors increase serotonin levels and increase of serotonin will inhibit the activity of involved enzymes in steroid producing of testicular tissue pass. This process leads to testosterone reduction [21] and this agrees with the results of current study. According to testosterone reduction through negative feedback process, GnRH secretion from hypothalamus and then LH secretion increases from anterior pituitary [22]. This agrees with the results of current study.

Findings of other researchers show that prolactin inhibits conversion of cholesterol to pregnenolone through increase of nitric oxide levels. It is also stated that some medicines from this family can increase cortisol levels [23]. Cortisol changes a number of LH receptors in Leydig cells and inhibits some available enzymes in pathway of steroids synthesis [24]. It is likely that increase of cortisol by Clomipramine can reduce testosterone synthesis.

However, the concentration of LH hormone in the experimental groups 3 and 4 has significant reduction compared to control and experimental group 1. This reduction is probably due to the consumption of ginger extract.

Also, the concentration of testosterone in the experimental groups 2, 3 and 4 has significant increase compared to experimental group 1. This reflects the positive role of ginger extract compared to the experimental group received Clomipramine alone.

It is stated in traditional medicine that ginger as a medicinal plant has a role in male fertility [25]. Gingerol, Shogaol and Sesquiterpenes are the most important compounds of ginger. Studies have shown that ginger extract also contains a large amount of selenium, vitamin A, B, C and E, flavonoids and glutathione [14, 15].

Studies expressed that in male rats, given to synthesis of Inhibin B by sertoli cells and increase of testosterone secretion, an occurrence of a negative self-regulatory reaction will be expected. This causes LH and FSH reduction and will effect on hypothalamus and GnRH-producing cells; and as a result the level of produced GnRH hormone decreases, which in turn reduces LH and FSH hormones [26]. Researches also suggested that phenylpropanoids and sesquiterpenes available in ginger extract effects on pituitary-gonadal axis, and thereby reduce the secretion of gonadotropin hormones [27]. This agrees with the results of the present study.

Studies expressed that gingerols and shogaols are androgens stimulators and can increase testosterone hormone [28]. Investigations showed that gingerols and sesquiterpenes inhibit arachidonic acid by inhabitation of lipoxygenase and cyclooxygenase pathways. And inhabitation of arachidonic acid synthesis, in turn leads to inhabitation of prostaglandins synthesis. Given to the role of prostaglandins in gonadotropins synthesis, the available compounds in ginger extract cause secretion of testosterone by negative self-regulatory effect of gonadotropins. So, increase of testosterone is observed by increase of ginger extract usage dose in experimental groups [29, 30]. This agrees with changes of testosterone in the present study compared to the Clomipramine groups.

5. Conclusion

In general, it can be said that Clomipramine medicine with the mentioned possible mechanisms has damaging effects on sexual hormones in male rats. So, special precautions should be done for consumption of Clomipramine in childbearing ages. Ginger extract due to having antioxidant properties and effective ingredients reduces damaging changes in sex hormones in rats treated with Clomipramine.

6. References

1. Sadock B, Sadock VA. Comperehensive text book of psychiatry. 7th ed, Baltimor lippincott Williams and Wilkins, 2000, 1441-1503.
2. Bancroft J, Munoz M, Beard M, Shapiro C. The effects of a new alpha-2 adrenoceptor antagonist on sleep and nocturnal penile tumescence in normal male volunteers and men with erectile dysfunction. Psychosom Med. 1995; 57(4):345-356.
3. Guiliano F, Rampin O. Central adrenergic control of penile erection. Int J Impot Res (suppl):S13-S19. 14. Blackwell B. Antidepressant drugs. In: Dukes MN Meyer's side effects of drugs. Elsevier, Amsterdam, 1984, 24-61.
4. Kaplan H, Sadock B. Baltimor synopsis of Psychiatry. 8th ed, Williams and wilkins. 1998; 609- 617.
5. Tatsumi M, Groshan K, Blakely R, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol. 1997; 340(2):249-58.
6. Blackwell B. Antidepressant drugs. In: Dukes MN Meyer's side effects of drugs. Elsevier, Amsterdam, 1984, 24-61.
7. Jones RB, Luscombe DK, Groom GV. Plasma prolactin concentrations in normal subjects and depressive patients following oral clomipramine. Postgrad Med J. 1977; 53(4):166-171.
8. Pomerantz SM, Hepner BC, Wertz JM. Serotonergic influences on male sexual behavior of rhesus monkeys: effects of serotonin agonists. Psychopharmacology (Berl) 1993; 111(1):47-54.
9. Rehavi M, Attali G, Weizman A. Suppression of serum gonadal steroids in rat by chronic treatment with dopamine and serotonin reuptake inhibitors. Euro. Neurosychopharmacology. 2000; 10:145-150.
10. Guay AT, Spark RF, Bansal S, Cunningham GR, Goodman NF, Nankin HR *et al.* Medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction. Am Assoc Clin Endocrinol. 2003; 31:621-27.
11. De Zeaan M, Nutziger DO. Effect of fluvoxamine on total serum cholesterol levels during weight reduction. J Clin Psychiatry. 1996; 57:346-348.
12. Jahan Tab A, Sepehri A, Mir Daylami Z, Arian Ghasemi E, Nouri S. Atacological investigation of medicinal plants of Ferulago angulate (schlecht) boiss in the Central Zagros Mountains (Kohkilooyeh area). Herbal Science Reasarches. 2012; 6(4):1-8.
13. Fallah Hosseini H. Effects of various extract of Silybum marianum seeds on α-glocosidase and α-amylase enzymatic activities in vitro conditions. Journal of Medicinal Plants. Specific edition No 7, 2012, 247-239.
14. Yang HS, Han DK, Kim JR, Sim JC. Effects of alpha-tocopherol on cadmium-induced toxicity in rat testis and spermatogenesis. J Korean Med Sci. 2006; 21(3):445-51.
15. Yanga CY, Chaob PDL, Houc YC, Tsaib SY, Wend KC, Hsiu SL. Marked decrease of cyclosporin bioavailability

caused by coadministration of ginkgo and onion in rats. J Food and Chemical Toxicology. 2006; 44:1572-1578.
16. Shukla Y, Prasad S, Tripathi C, Singh M, George J, Kalra N. *In vitro* and *in vivo* modulation of testosterone mediated alterations in apoptosis related proteins by [6]-gingerol. Mul Nutr Food Res. 2007; 51(12):1492-502.
17. Khaki A, Nouri M, Fathiazad F, Khaki A. Evaluation of Zingiber Officinalis and Allium Cepa on spermatogenesis in rat. Medical Journal of Tabriz University of Medical Sciences. 2008; 30(2):53-8.
18. Bhattaria S, Tran VH, Duke CC. The stability of gingerol and shogaol in aqueous solutions. J Pharm Sci. 2001; 90(10):1658-64.
19. Hayes Frances, Decrttz J, William S, Prolactin F. LH, FSH and TSH responses to a dopamine antagonist, The Journal of Clinical Endocrinology & Metabolism. 2003; 86(I):53-58.
20. McCann, Kimura SM, Walczewska M, Karanth A, Retiori S, Yu V *et al.* Hypothalamic control of FSH and LH by FSH-RF, LHRH, cytokines, teptin and nitric oxide, Neuroimmunomodulation. 1998; 5:193-202.
21. Hajak G, Rodenbeck A, Alder L. Nocturnal melatonin secretion and sleep after doxepin administration in chronic primary insomnia. Pharmacopsychiatry. 1996; 29:187-92.
22. Guyton Arthur, C. Hal John, E. Textbook of Medical Physiology 2010; 597-702.
23. Dobashi M, Fujisawa M, Yamazaki T, Okuda Y, Kanzaki M, Tatsumi N *et al.* Inhibition of steroidogenesis in Leydig cells by exogenous nitric oxide occurs independently of steroidogenic acute regulatory protein (STAR) mRNA. Systems biology in reproductive medicine. 2001; 47(3):203-209.
24. Hartters, Grozinger, weigmann H, Roschkej, Hiemke C. Increased bioavailability of oral melatonin after fluvoxamine coadministration. Clin Pharmacol Ther. 2000; 67:1-6.
25. Grzanna R, Lindmark L, Frondoza CG. Ginger--an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005; 8:125-132.
26. Norman JF, Way JM. Some ecological observation on the use of date pollen in hypothalamic hormones. Endocrinol. 1998; 2:532-548.
27. Rahmanian F, Hemayat Khah Jahromi V, Kargar H. The effects of ginger hydroalcoholic extract on spermatogenesis process and hormone-pituitary-gonadal axis in immature mice. Journal of Science of Teacher Training University. 2012; 10(3):915-922.
28. Khaki A, Fathiazad F, Nouri M, Khaki AA. The effects of Ginger on spermatogenesis and sperm parameters of rat. Iranian Journal of Reproductive Medicine. 2009; 7:7- 12.
29. Murakami A, Takahashi D, Kinoshita T *et al.* Zerombone a shoutheast Asian ginger sesguiterpene, markedly suppresses free radical generation, proinflammarory protein production, and cancer cell proliferation accompanied by apoptosis: the alpha, betaunsaturated carbonyl group is a prerequisite. Carcinogenesis. 2002; 23950:795-802.
30. Yogeshwer SH, Sahdeo P, Chitra T, Madhulika S *et al. In vitro* and *in vivo* modulation of testosterone mediated alterations in apoptosis related proteins by [6] - gingerol, Science Direct. 2007; 168:1492-1502.