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Effects of Hypericum Perforatum on Histology of the Testes and Sex Hormones of Male Rats

Adil Abdulrahman Mustafa[1], Khalaf Nahar Ahmad[1], Yasir I Abbass[2], Azzawi M Hadi[3*]

[1]Tikrit Agricultural College, Department of Food Industries, Iraq
[2]Tikrit Medical College Department of Surgery, Iraq
[3]Ninevah Medical College Department of Surgery, Iraq

Corresponding Author: Azzawi M Hadi
Email: azzawihadi@gmail.com

ABSTRACT
Hypericum perforatum also known as St. John's wort had many components that have been proved to be biologically active. A double blind controlled experimental study tried to highlight the effect of Hypericum perforatum tea preparation on rat male sex hormones and testicular histology. Twenty-five male rats had been divided in to 3 experimental groups each group had 7 rats, exposed to 3 different dose concentration for each group. The control group was 4 rats that exposed to the same feeding and environmental conditions of the other groups. Hypericum perforatum tea was prepared and diluted to a dose of 3,6, and 9 cc/kg per day. Each dose was given to one experimental group for one month with water supply. There was a noticeable increment in testosterone, LH,FSH, and decrement in male estrogen, and thyroid function levels in comparism between experiment groups and control group, as well there was histological changes that could promise to use Hypericum perforatum in treatment of male infertility.

Keywords: Hypericum perforatum, St. John's wort, sex hormones, infertility.

Correspondence:
Azzawi M Hadi
Ninevah Medical College Department of Surgery, Iraq
Email: azzawihadi@gmail.com

INTRODUCTION
Herbs were a major part of ancient customary medicine, trials revealed efficacy in relieving symptoms, these facts made the tendency to use and investigate different types of herbs annually. *Hypericum perforatum* tea used by middle aged and elderly to control diabetes and lipid profile, this point drags our attention to evaluate the effect of this prepared tea on fertility related hormones and the histology of the testis. *Hypericum perforatum* has a kinship to Hypericaceae, publicized as St. John's wort (SJW), that had been utilized as a remedy in various eastern nations [(1)]. Flavonoids, phloroglucinols, and naphthodianthrones, are main bioactive components that have been documented to treat mild to moderate depression and it clouts the serotonergic system, and down regulate of proinflammatory cytokine [(2, 3, 4, 5)].

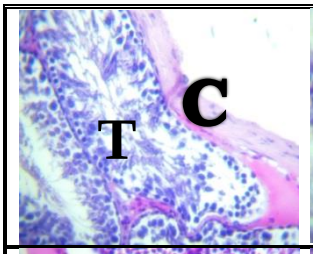
The water soluble (hydrophilic) arm of polyphenols enhances the immunity by stimulation of mononuclear part of immune system, i.e. the cellular immunity, as well as activation of humoral immunity, in contrary the lipophilic arm exhibited immune-inhibitory action [(6)]. *H. perforatum* reduced rat's lipid profile by lowering the levels of total cholesterol, triglycerides, and LDL cholesterol, and increasing the level of HDL cholesterol. In addition, SJW extracts increase the activity of catalyzing enzymes as catalase and superoxide dismutase [(7)], as well it improves the glycemic index of diabetics, and improves sugar control [(8)].

H. perforatum's inhibits the level of malondialdehyde (MDA is the marker of oxidative stress activity). However, catalase and glutathione peroxidase activity increased (GSHPx the enzyme that protect cells from oxidative damage) [(9)].

The study aimed to demonstrate the effect of *H. perforatum* tea on the male rat gonads, and sex hormones melieu.

MATERIALS AND METHODS
A double blind controlled experimental study tried to highlight the effect of Hypericum perforatum extracts prepared as a tea on rat male sex, and thyroid hormones and testicular histology. Twenty-five male rats had been divided in to 3 experimental groups each group had 7 rats, exposed to 3 different dose concentration for each group. The control group was 4 rats that exposed to the same feeding and environmental conditions of the other groups. Hypericum perforatum tea was prepared by boiling 250 grams in 4 litters of water, until half of the water have been evaporated, the same procedure of preparation was used in the traditional medicine in Iraq, and the resulted tea is used to control diabetes and hyperlipidemia. The patients used the prepared tea in a dose of 250cc twice daily, so that we give a dose of 6cc/kg per day as comparable dose, 3cc/kg per day as the lower dose, and 9cc/kg per day as a higher dose. Each dose was given to one experimental group for one month with water supply. After 1 month of treatment we perform serum levels of Testosterone, estradiol, FSH, LH, and Thyroid hormones (TSH, T3, T4), as well the histological changes of testicles for all rats.

RESULTS
The testes of the control group were covered by a dense connective tissue capsule which send trabeculae to the interstitial area of the testes to form the lobules that contained semineferous tubules.



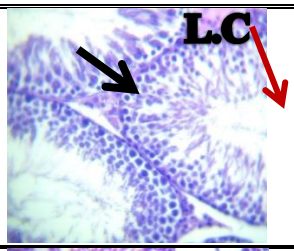
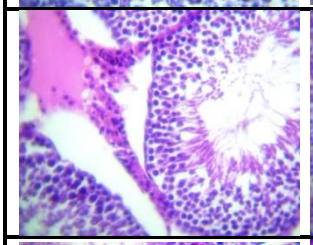


Figure 1: histology of testis of the control group. T=tubules, C= capsule, L.C=Leydig Cells, red arrow= Lumen



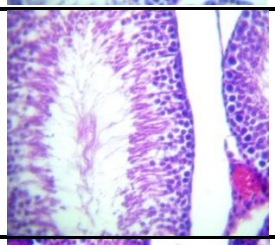
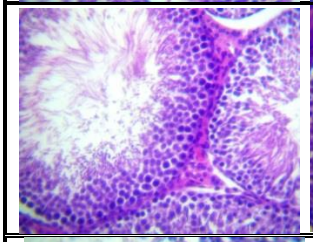


Figure 2: Testis of the group that have been treated with the low dose of Hypericum perforatum tea.



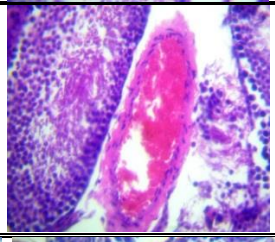
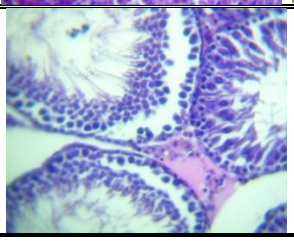


Figure 3: Testis of the group that have been treated with the moderate dose of Hypericum perforatum tea.



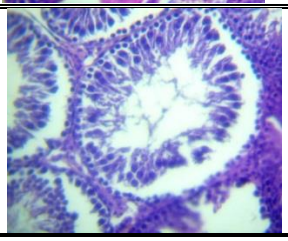


Figure 4: Testis of the group that have been treated with the high dose of Hypericum perforatum tea.

Semineferous tubules had basement membrane on it the spermatogonia were resting. The second row of cells in lumen were the larger primary spermatocytes, while the third row formed by secondary spermatocytes, followed by fourth row which formed by the spermatids, that appears smaller and denser cells. Spermatids transformed into sperms that appear in the Semineferous tubules lumen as wavy bundles. Among the semineferous tubules, a group of Leydig cells (interstitial cells) were found, which produce testosterone.

Testis of the group that have been treated with different doses of Hypericum perforatum tea shows congested subcapsular blood vessels, and there is variable populations of sperms from one lumen to another, with atrophied Leydig cells which were surrounded by many congested blood capillaries.

Table 1 shows the hormonal changes between control and study groups. There was a noticeable changes in hormones levels as shown in table 1, testosterone, FSH, LH, are increased in low (conc1) and moderate (conc2) Hypericum perforatum tea concentrations as compared with the control group, but in high Hypericum perforatum tea concentration (conc3) these hormones have lower levels than moderate(conc2) Hypericum perforatum tea concentration, but still higher than control and low concentration(conc1).

Table 1: results of hormonal assessment of control and study groups that treated with three different concentrations of Hypericum perforatum tea.

Cases	Control	Conc 1	Conc 2	Conc 3
Testosterone (SD)	0.657(0.148)	0.972(0.082)	1.188(0.125)	1.161(0.083)
LH(SD)	0.795(0.112)	1.076(0.137)	1.159(0.17)	1.104(0.029)
FSH(SD)	0.8425(0.062)	1.173(0.09)	1.25(0.056)	1.106(0.0465)
Estradiol (SD)	80.675(8.42)	34.37(5.428)	31.01(5.367)	45.871(7.416)
TSH(SD)	0.00575(0.0015)	0.0061(0.004)	0.0065(0.0045)	0.0064(0.005)
T3(SD)	2.611(0.09)	0.526(0.119)	0.53(0.766)	0.766(0.13)
T4(SD)	2.07(0.24)	1.666(0.306)	1.127(0.549)	1.627(0.656)

Estradiol is decreased in low (conc1) and moderate (conc2) Hypericum perforatum tea concentration as compared with the control group, but in high concentration (conc3) tea this hormone stepped up more than low (conc1), and moderate(conc2) Hypericum perforatum tea concentration, but still lower than control group.

TSH increased in all Hypericum perforatum tea concentrations to a little bit higher levels as compared with control group. While T3, and T4 were decreased in

low and moderate concentrations, and increased but still lower than control in high concentrations of Hypericum perforatum tea.

DISCUSSION

Using herbal remedies as substitution of, or in combined with chemical medicines is an ancient attitude, and increasingly existed. The low cost and minimum side effects, with an accepted result in many cases encourage their use. Hypericum perforatum is an example this remedy, which used by diabetics to improve glucose lipid control.

Flavonoids, the main components of Hypericum perforatum, is a numerous set of polyphenols, made up of more than five thousand of different plants produced composites. [10] Ingestion of flavonoids was well known to enhance heart and circulatory system, as well lessen the hazard of diseases that could affect this system (cardiovascular), by ameliorating the function of endothelium, and significantly down the levels of blood pressure in both systolic and diastolic measures.[11] These 2 effects improves peripheral and cerebral blood flow. Which gives a protective effect against cardio- and cerebrovascular disease. Endothelial function sketched as vascular responses conciliated by mediators that released from the endothelium which causes of vasodilation or vasoconstriction.[12] The flow-mediated dilation (FMD), is a non-invasive procedure used for measurement of the function or dysfunction of Endothelium, FMD is now regarded best way for measurement of endothelial function[13]. High FMD, which means improved function of blood vessels, after the intake of a variable diets rich in flavonoid was documented [14]. In vivo measurement of endothelial function, by FMD, detects an effective bioavailability of nitric oxide, and that was the cause of improved in FMD response after flavonoid intake. this suggests an increment of the endothelial nitric oxide's levels and activity, in the blood vessels endothelium[15], these events can explain the dilated capillaries in serial sections of testicles, which could play a role in improved nutrition of the tubules and hence the developing sperms.

The flavonoids were thought to be correlated to carcinoma of breast because they have estrogens like structure, so it is regarded as phytoestrogen, this may open the door to explain so some of hormonal effect of these components. It had been documented that consumption of flavonoid in child bearing age women had little effect on most serum sex hormones, but it leads to lower the measures of dihydroepiandrosteron and dihydroepiandrosteron sulphate which are weak androgen as well they are testosterone precursors [16].

Thyroid function was affected by Hypericum perforatum tea in all doses, there is reduction in thyroid hormone levels, to a noticeable level. Flavonoids affect T3, and T4 biosynthesis, thus play a vital anti-thyroid effect. Goiter can exist as a side effects but are not usually noticed among people fed on flavonoids rich diet [17]. Flavonoids can suppress thyroperoxidase activity which reduces the levels of plasma T3 and T4. It was also noticed that flavonoids extracted from green and black tea can change the function and structure of the thyroid, which get enlarged by thyroid follicles [18].

It can be concluded that Hypericum perforatum could affect the fertility level, as well the potency of the persons used, further studies with larger number, with investigation of seminal parameters, and seminal oxidative stress.

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