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Outcome Of Hypericum Perforatum Tea Consumption On Liver Enzymes And Histology

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Abstract.

Hypericum perforatum(HP)is an example such remedies, that prescribed to diabetics to control the levels of glucose and lipid. Three groups of 7 albino rats were subjected to HP extract in the form of a prepared tea in a doses of 3cc,6cc,9cc/kg body weight given orally with drinking water, the control group of 4 rats were live in the same environmental conditions.At the end of the study period which was 30 daysanimals were sacrificed, blood aspirated to assay the liver enzymes, named alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH), andstatistically compared to the enzymes of the control group. Liver tissue examined microscopically to determine the histological changes associated with the experiments. While the ALT, AST, LDH activities were reduced in the lower dose of HP tea, it started to increase with the moderate and high dose of that preparation. There was a progressive histological changes of liver tissue with the increased dose of HP tea. With the higher dose the was tissue necrosis and karyolysis of the nuclei as well infiltration of lymphocyte and kupffer cells.This lead to conclusion of a progressive liver damage with increased dose, that should be taken in consideration when use this remedy.

Keywords: Hypericum perforatum, St. John's wort, liver function, liver enzyme, hepatotoxicity.

Introduction

Since early days of life ,herbal medicine had been utilized as complementarymedicine[1]. Theyusedas substitute of, or in combination with chemical medications. This old approach, had return to the light spot. The lowerpriceand side effects, with agiven a positive responseresulted in a lot of patients motivatetheir usage. Hypericum perforatum(HP) is an example such remedies, that prescribed to diabetics to control the levels of glucose and lipid[2].Researches revealed that herbal purified extracts, had many important compounds asphenolic and flavonoids composites as well principle oils, that

distillated from herbshad many biological actionslike anti-microbs, anti-inflammation, depression control effects and scavenger oxidation activity[3,4].

Hypericum perforatum (HP) popularly known as St. John's wort (SJW), it is mention on the top of the list of the indispensible medicinal plants, thathad flavonoids and phenolic contents , which have been shown to exert an efficient anti-inflammatory and antioxidant effects on animal with induced acute inflammation[5]. HP isstill used in Turkey, as adrug to enhance healing of ulcers, control diabetes, supportive measure in aflu cases, lower gastrointestinal symptoms, liver and bile ductdiseases, and cases of jaundice[6]. It was reportedthatalcoholic extracts of HP exert a protective activityon liver cells of the rats[7].

The effects of Hypericum perforatumtea (HP) on liverhistology and function was investigated to highlight any evidence of hepatotoxicity which was the aim of this study.

Material and Methods:

A double blind controlledexperimental study designed to highlight the consequenceof water soluble Hypericum perforatumextractsmadeas a tea on theliver function and histology of the rats. Twenty one rats had been dividedinto 3 study groups everygroup consist of 7 rats, these study groups weregivena different concentration of H. Perforatum tea for each group. Another groupof 4 ratsnursed as a controlgroup, this group get the samefood and live in the same environmentlike the other groups. HP teaprepared byadmixingone forth kilogram of H. perforatum in four litters of water, the mixed was boiled until evaporation of half of the water, this was the preparationway that considered by the diabetics in ourlocality. This teaproposed to improve the control of sugar and lipidlevels in these patients. The recommendeddose of the tea was 250 cc two times a day, so thecomparabledose for the rats wascalculated to be 6cc/kg a day . the doseof , 3cc/kg/day and 9cc/kg/day given as the lower and higher dose respectively. eachstudy group nursed by one of these doses of the teafor 30 days mixed with water supply. At the end treatment period ALT,AST, and HDL weremeasured and compared. Histology ofliver of the study groups also compared to thecontrol.

Statistical analysis done by two tailed student T test using SPSS program to compare the results of the experiment groups with the control group.

Results:

Histology of the liver of the control group.

Figure (1) shows histology of the control group, in which the parenchyma of the liver was formed bypolygonal liver cells arranged in columns toward the central vein that found in the center of liver lobule. Each cell have a spherical nucleus with one or two nuclei and acidophilic cytoplasm, in between

the hepatocytes there was a network of blood sinusoids with kupffercells.The portal area presented nearby each lobule formed by a branch of portal vein hepatic artery and bile duct surrounded by interstitial connective tissue and infiltrated bymany lymphocytes.

Histology of the liver of the low dose HP tea(HP1) group:

Figure (2) shows histological changes of the liver of HP1 group, we can notice the parenchyma ofliver was a occupied with a polygonal liver cells with spherical basophilic nucleus, some of these cells where arranged in columns, and others I groups around each central vein. The blood sinusoid contain many kupffer cells, and the portal area of liver lobules had lymphocytic aggregation around the branch of portal vein hepatic artery and bile duct, these lymphocytic aggregation where also demonstrated in a small foci between liver cells.

Histology of the liver of the moderate dose HP tea(HP2) group:

Figure (3) shows histological changes of the liver of HP2 group, its obvious that the liverparenchyma was formed by a polyhedral hepatocyte which was arranged in the form of cords and others in groups and this whole cells appeared normal in shape and had eosinophilic cytoplasm with basophilicsphericalnuclei. Many blood sinusoids presented like a network with the presence of large size and number of kupffer cells, the central vein of each lobule seen empty, while the branches of portal vain were congestedwith blood in the portal area, which also contain branches of hepatic artery and bile duct surrounded by discrete lymphocytes.

Histology of the liver of the high dose HP tea(HP3) group:

Figure (4) shows histological changes of the liver of HP3 group, it is evident that the liver cells'parenchyma weredegenerated associated with karyolysis of the nuclei and some cells had a lost nuclei (ghost-like) picture. The blood sinusoid contained many kupffer cells of large sizebetween liver cells, while a fociof lymphocytic aggregation were noted around these liver cells. The central veins and veins of portal area where congested with the blood and surrounded with many white blood cells especially the lymphocytes. The subcapsular zone was containing degenerated and necrotic cells with pyknotic nuclei. These changes suggested a damage of the liver cells.Table (1) summarized the histological changes with of different dose oh HP tea. It tails that the higher the dose of HP concentration, the higher the damage of liver cells, for the same duration.

It had been noticed in table (2) that with a low dose of HP tea there was a progressive increase in liver enzymes (ALT,AST, and LDH) as compared with the control group. This rise was more prominent with ALT, though the difference was statistically non-significant.

With the high dose of HP tea the liver enzymes readings spiked up, to reach a significant level of difference as compared with the control group.

Discussion.

Many types medicines are metabolized in the liver, this may produce liver toxicity that induced by these medications. Liver toxicity is very important clinical conditionwhich may lead to a lethal sequel of liver failure, that may necessitate an urgent transplantation[8].

Although Hypericum perforatum proposed to give a hepatoprotection[9], some reported cases show a hepatotoxicity of HP preparations[8].The hepatoprotection in a preliminary treatedrats with HPextract in a dose of 50 mg/kg, before induction of ischemia and reperfusion state. The treated arm of the experiment significantly hadreduced activities of liver enzymes ALT, AST, LDH compared to animals with induced Ischemia Reperfusion without treatment–control group.Liver ischemia reperfusion produce a free radicals that lead to increase the oxidative stress in liver cells, H. perforatum that have an antioxidant activities play a role in maintenance of the fineequilibriumofantioxidant scavenging roleand the continually produced free radicals to predominate the power of thebody antioxidant guarding systems[9].

It had been proposed that HP extract may induce hepatotoxicity by interfering with the action on cytochrome P450, this enzyme maypromote clearance of some drugs or directly decrease their levels in the serum.HP extract may interact with other medications that may be taken synchronously and increasetheirside effects, as liver toxicity. Fortunately, bilirubin and liver enzyme and levels decline gradually after termination of intake[8].

It was believed that many factors were involved in pathogenicity of hepatic injury of pathogenicity. Some of these factors are oxidative stress, inflammatory process and immune mediated reactions.

High levels of ROS may activate kappa B nuclear factor (NF-κB), that's subsequently induce nuclear translocation, which are responsible for modulation of liver injury by regulation of production of inflammatory mediator (cytokines), tumor necrosis factor-α alpha is an example of such cytokines, that induces enzymes that modulate inflammatory process. [10,11]

Heating of vegetables may oxidize , break, and separatethe active bio-compounds[12]. Heat treated food may lead to a positive and negative effect, which have been found to be depended on the morphology of the vegetables and their nutritional properties, as well the duration and degree of heating process. These factors lead to variable effects on the antioxidant properties of the food[13,14]. The antioxidant properties may declined with heating by destruction of the antioxidant materials or by

the newly formed pro oxidant compounds, this may cause a deleterious effect on the living cells. On the other hand the altered structure of the newly formed antioxidants as well the formation of unique antioxidant compounds that may amplify the origenal antioxidant condition[15,16], such results pointed that heat may promote antioxidant profile in fruits and vegetables. However, anearlier reports suggested that, the antioxidant profile of many food materials will be declined if they got a heating to a level between 65- 100C[14]. Some chemical materials can induce oxidative stress in the living tissues, these are known as the pro-oxidants. They conduct this task via either production of reactive oxygen species or by inhibition of the existed antioxidant. Surprising fact is that, some of the well-known antioxidants were commanded to havea prooxidantactions. Some determinant factors can enhance the alteration of antioxidant agents to a pro-oxidant; these factorsinclude the level of metallic ions in the composition of the antioxidant, the quantity of that antioxidant in the environment of the tissue, as well the oxidation-reduction (redox) potential of the antioxidant in that milieu[17]. This may explain the liver damage caused by the high dose tea of HP3 that have been boiled for long time.

The progressive significant increase in liver enzymeslevels as the dose of HP tea increased tells that some sort of liver insult had occurred. This increment was more prominent in ALT and AST. LDH raised levels was not so high as compared with control.

Alanine transaminase (ALT) and Aspartate transaminase (AST)areenzymes that regarded as a sensitive markersof liver cellsdamage, unfortunately they are regarded nonspecific because they are produced by other tissues (muscle, renal, and red blood cells). AST had a higher level in liver cells cytoplasm, as compared with ALT. However, as AST is removed more rapidlyin plasma , it's level is less than ALT. These enzymes may be raisedin some conditions as cirrhosis,acute viral liver infection, chronic inflammatory conditionsaffecting the liver, alcoholic liver injuries, and liver ischemia[18].

Lactate dehydrogenase (LDH) is an importantenzyme for non-aerobic cell respiration. It is produced in conditions of cell hypoxia. Hepatocytes' production of LDH reflected the levelof liver cells' hypoxia. In case of acute liver failure, macrophage proliferated, LDH production will increased.theraised LDHlevels in hepatitis patients had been consideredas a consequenceof enzyme leakafterhepatocytes damage. The importanceof LDH in hepatic disease had been supposedto be lowerthanALT because of the extensivepresence of cells that producing LDH in the whole body. The congestive liver as well the shocked liver, wereassociated with reduced oxygen delivery to the hepatocytes andmarkedrisesin LDHreading [19]. The above scenarios may explain the cause behind elevation of liver enzymes by direct hepatotoxicity, or indirectly by liver hypoxia.

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Figure (1) liver histology of the control group.

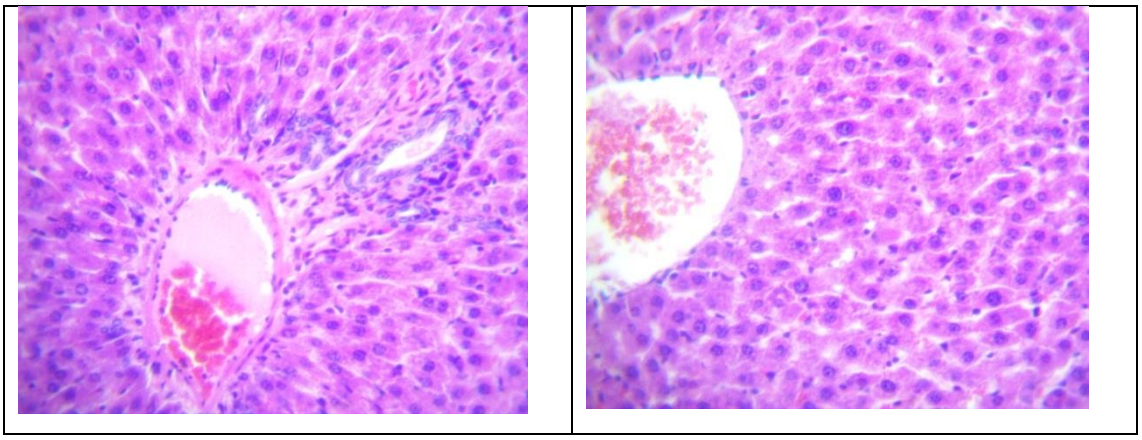

Figure (2): Histological changes of liver of the low dose HP tea group. HP1.

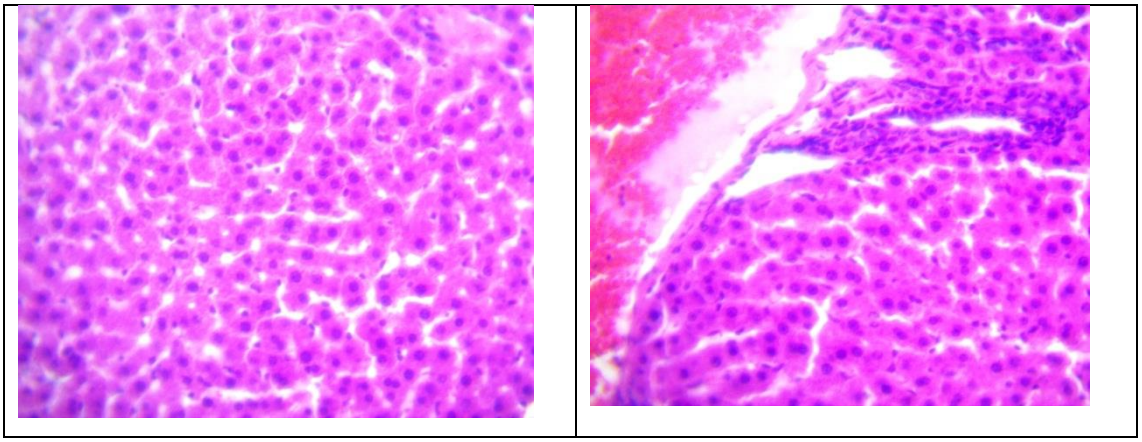

Figure (3): Histological changes of liver of the moderate dose HP tea group. HP2.

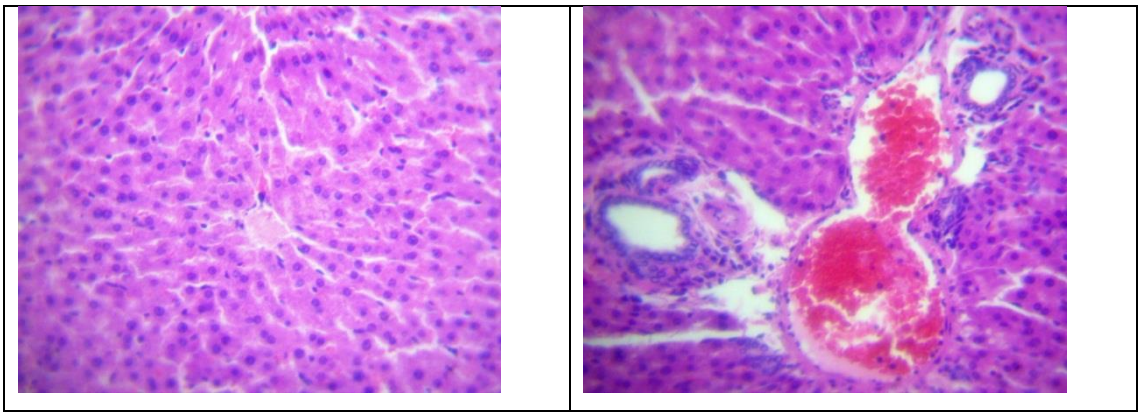

Figure (4): Histological changes of liver of the high dose HP tea group. HP3.

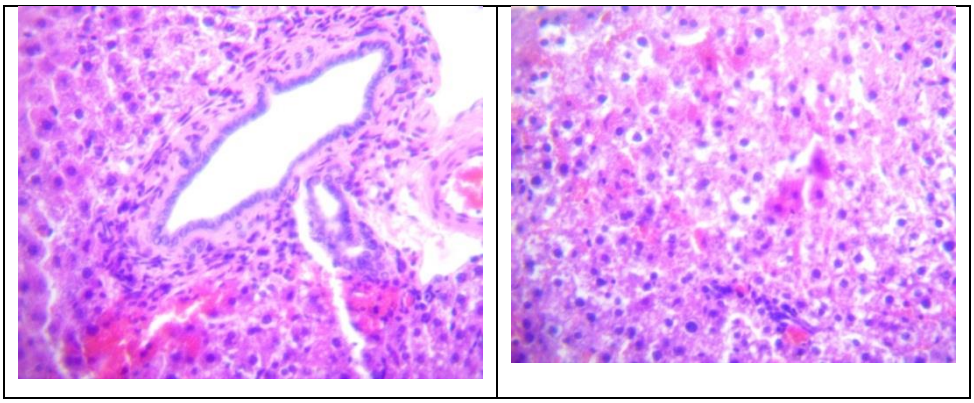

Table (1) Summary of histological changes associated with different concentrations of HP tea consumption.

	Liver cells	Nucleus	Portal area	lymphocytes	kupffer cells
Control	polygonal	Present	Normal	Scattered	Normal
HP1	polygonal	present	Normal	Infiltration	Normal
HP2	polyhedral	present	Congested	Small foci	Many large size
HP3	Degenerated, necrotic in subcapsular zone	Karyolysis, and pyknotic	Congested	foci	Many large size

Table (2) Liver enzymes of control and study groups treated by HP tea.

	ALT Mean(SD) **[t. value]**	**AST** Mean(SD) **[t. value]**	**LDH** Mean(SD) **[t. value]**
Control	50.25(1.708)	55.75(2.5)	177.5(3.11)
HP1	64.43(2.225)*	74.143(2.268)	201.57(4.353)*
HP2	74.143(2.268)*	77.283(2.498)**	212.286(3.729)*
HP3	92.143(4.259)***	96.571(5.769)***	235.14(5.398)*

*p<0.05, **p<0.01, ***p<0.001