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DETERIORATION OF LIVER FUNCTION BIOMARKERS INDUCED BY ST. JOHN'S WORT

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ABSTRACT
St. John's Wort (SJW) is an alternative herbal treatment for anxiety and depression. Among the dose-limiting side effects of this plant is photosensitization. This study was designed to examine the potential adverse effects on hepatic function caused by exposure of laboratory rats to SJW. In this experiment, thirty adult rats were distributed into three groups, each containing ten. The first group (CON) was for control; in the second group (SJW1) the animals were provided with St. John's wort without direct exposure to sunlight, and in the third group (SJW2) the animals received SJW with direct exposure to sunlight. The treatment period lasted fifteen consecutive days, and on the sixteenth day, the animals were dissected, blood samples were collected, and serum liver enzyme indicators (ALT, AST, and ATP) were analyzed. Results demonstrated a considerable rising in liver function indicators levels for rats dosed with the extract and exposed to direct sunlight (SJW2) compared to the control (CON) group. It was concluded that this plant has a toxic effect on liver function at excessive doses and exposure to sunlight, causing photosensitivity in vivo.

KEYWORDS: blood samples, liver enzyme, laboratory rats.

INTRODUCTION
Liver damage may be induced in vivo by excessive or prolonged exposure to drugs, chemicals, or even medicinal plants.[1-3] This often leads to a malfunction of the liver and it is unable to perform its activities properly.[4,5] Many studies have proven that exposure to medications outside the health standards for use can turn into toxins for the body.[6-8] The liver is one of the primary organs that react to these toxins and may result in liver failure.[9] Secondary or hepatic photosensitivity is a description of any liver toxicity that leads to a decrease in the liver's ability to metabolize any chemical that causes sensitivity to light. It is more common than primary photosensitivity and may be caused by eating plants that contain compounds that are toxic to the liver.[10,11]

Toxic compounds found in many light-sensitive plant species are well known, but remain unknown in others. It is worth noting that several chemicals are considered photosensitizing agents, including plant origin.[12,13] Since ancient times until the present time, many residents of developing countries have resorted to medicinal herbs for the prevention and treatment of various diseases due to their availability, cheapness, and safety in terms of their low side effects.[14-16] In addition, in several developed countries, there is a wide demand for medicinal plant supplements as an alternative to chemical medicines, and many in vivo study experiments have proven their preventive and therapeutic efficacy against various pathogens.[17,18] St. John's wort, scientifically called *Hypericum perforatum L*, represents an alternate remediation for bouts of depression.[19] It is a perennial herb with golden yellow flowers that consists of complex and biologically active compounds. It is sold as a dietary supplement and is commercially available in several forms such as tablets, capsules, and teas.[20] It has been employed medicinally for centuries, and its oil preparations can be utilized topically to remedy burns, wounds, and minor inflammatory skin problems.[21] It is considered one of the most widely used antidepressants as an over-the-counter treatment by a high percentage of the population in some countries.[22] Therefore, due to the growing use of this herbal remedy, it is important to clarify and confirm the potential drug harm that it may cause in excessive doses to the body. Therefore, the object of this experiment is to assess liver dysfunction caused by this extract in a rat model.

METHODOLOGY
Medicinal plant
Solgar St. John's Wort standardized full potency, high quality herbal extract (made in USA). Recommended use as an herbal dietary supplement for adults. They are free

vegetarian capsules without use of artificial preservatives, flavors or colors.

Laboratory rats and study design

In this experiment, thirty male rats, aged approximately (17-23) weeks and weighing (190-230) grams, were consumed from laboratory animal centers and homes. They were carefully placed in designated cages under high-quality laboratory conditions in terms of temperature, light/dark cycles, ventilation, and easy access to food and water ad libitum. They adapted to environmental circumstances for (7) days before carrying out the work. In the eighth day all rats were distributed into (3) groups (n=10 / group) as described in Table (1). On the sixteenth day, the anesthetized animals were sacrificed, collecting blood samples using a heart puncture device, placing them in special tubes, and sera were isolated from all the studied rats to complete the procedures for testing liver indicators.

Table 1: Animal groups and treatments.

Groups	Experiment treatments lasting 15 uninterrupted days
CON	Healthy rats for control
SJW1	Rats provided with St. John's wort at 3mg/kg by oral gavage, without exposing them to direct sunlight.
SJW2	Rats administered SJW at 3mg/kg by oral gavage, with exposing them to direct sunlight for half an hour [23] between 10-11 am.

Measurements of hepatic indices

Blood samples were collected in specialized sterile tubes, and centrifuged at 3500 rpm (10 min), and then sera were obtained to store at an appropriate temperature until serology tests were performed. Serum liver enzymes were used by diagnostic instruments (Roche) in an automated instrument.

Data analysis

The data were statistically analyzed using SPSS and Microsoft Excel XP, and presented on an easy measure of mean ± standard deviation. To confirm the differentiation between values of groups, analysis of variance (ANOVA) test was used followed by Duncan's multiple post hock. A probability less than 0.05 was set as important.

RESULTS

The impact assessment of St. John's Wort on liver function in laboratory rats showed that SJW with direct exposure to sunlight led to a notable ($P < 0.05$) augmentation in liver enzymes concentration (ALT, AST, and ATP) in SJW2 group (140.06±3.87; 151.34±4.75; and 318.31± 6.74 respectively) when compared to CON group (91.41±4.14; 106.12±5.71; and 201.53±7.17 respectively). However, no clear difference was recorded between the rats dosed with this extract without exposing them to sunlight (SJW1) compared to control rats as shown in figures.[1-3]

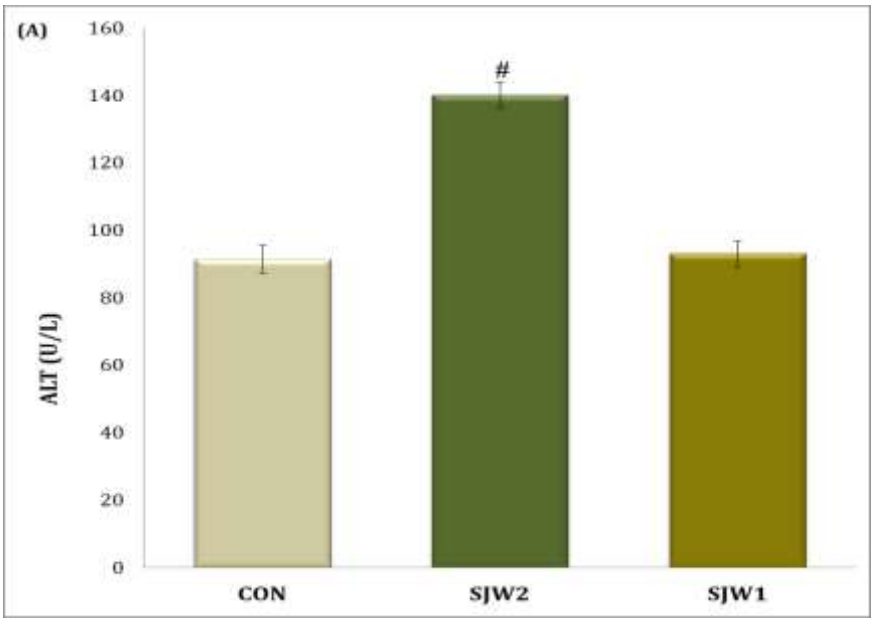

Figure 1: The effectiveness of SJW on of serum alanine transaminase (ALT) level for all rats studied. The symbol (#) indicates significant variance when compared to control rats.

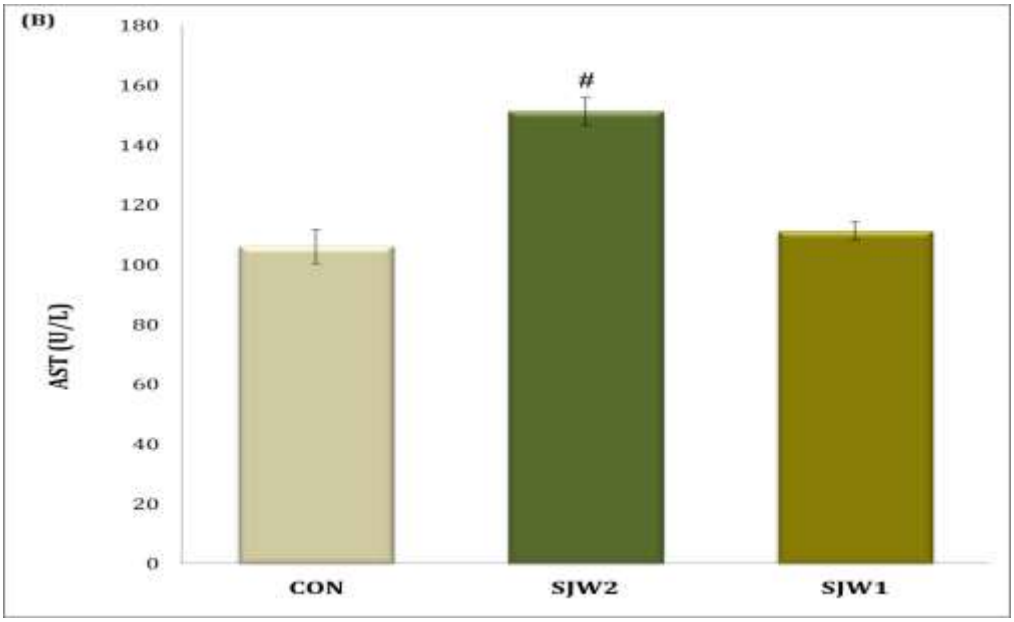

Figure 2: The effectiveness of SJW on of serum aspartate aminotransferase (AST) level for all rats studied. The symbol (#) indicates significant variance when compared to control rats.

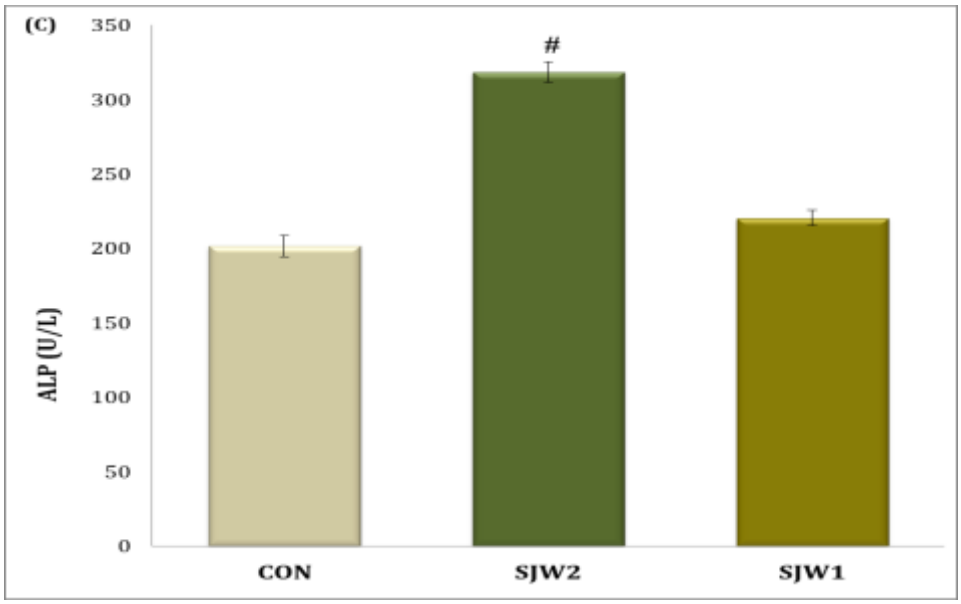

Figure 3: The effectiveness of SJW on of serum alkaline phosphatase (ALP) level for all rats studied. The symbol (#) indicates significant variance when compared to control rats.

DISCUSSION

Recently, researchers have pursued natural compounds that can effectively help in managing diseases without any side effects.[24-26] One of these herbal remedies is St. John's wort, which is used to this day traditionally to treat depression and relieve disturbed moods.[27] Hypericin is the main component of this herb, and represents a natural chromophore that has historically been used for medical use because it is believed to have antidepressant, antimicrobial, and antiangiogenic effects.[28,29] However, it has been recognized as a major photodynamic toxin. Meaning, it is a phototoxic substance that enters the blood vessels after ingestion and is stimulated by shining sunlight. The chemical construction of hypericin is affected by sunlight, which makes it a toxic compound and it is activated by ultraviolet rays, causing photosensitivity in the body.[30] The phototoxicity of hypericin is strongly oxygen dependent, as no such effects are found in hypoxic conditions.[31] This explains the results of the current experimental study, where it was noted that rats dosed with the medicinal plant exposed to direct sunlight for half an hour and for 15 uninterrupted days were negatively affected and showed signs of liver dysfunction through a noticeable increase in the levels of serum liver enzymes. This indicates the spillage of these

cytosolic enzymes and their transfer into the blood circulation, due to the destruction and damage of liver cells and the insufficiency of liver function due to alteration penetrability of hepatocytes membrane.[32,33]

It is known that the liver is the target organ for toxic substances, and therefore it is exposed to different types of oxidative stresses, and therefore any defect in the function of liver cells can lead to a change in the components of blood serum and the functions of enzymes.[34,35] In clinical studies, elevated levels of AST, ALT, and ALP, released into the circulation by damaged liver cells, are linked with liver dysfunction.[36-38] Toxins found in some plants are thought to damage liver cells and prevent the secretion of phylloerythrin which then accumulates in the general circulation.[39] Besides, there are many molecules, especially pharmaceutical ones that absorb ultraviolet as well as visible rays.[40] Chlorophyll-derived phylloerythrin is eventual main photosensitizer in hepatic photosensitization in the body. It is a strong photosensitizer, but has no significant effect because it is quickly eliminated through bile.[41] In a damaged liver, assembled phylloerythrin in peripheral circulation at low levels, in combination with sunlight, is sufficient to induce photosensitivity.[42] From the above, Photosensitization occurs when phototoxic compounds produced in plants or their metabolites become biologically available within the body after ingestion.[43]

CONCLUSIONS

Results of this experimental study, was concluded that St. John's wort has a damaging ability on hepatic cells and disrupts liver function at high doses and exposure to direct sunlight in vivo.

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