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Biological changes in liver, kidney and serum indices in rats treated with ethanolic extract of *Crateagus azarolus* areal parts

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Abstract: This study evaluates how the ethanolic areal extract of *Crateagus azarolus* affects the biochemical and functional characteristics of the liver, kidney and serum. Two groups of albino male rats (n1=6, n2=6), were given 400 mg/kg of *C. azarolus* ethanolic extract orally daily for two weeks, whereas the control group was given saline. The animals' necks were translocated, blood samples collected, and the liver, kidney and heart removed, and their relative organ weight (ROW) calculated. Analysis of serum parameters showed that liver enzyme ALT and AST increased significantly (58%) in *C. azarolus* treated group, whereas ALP and total bilirubin dropped (27%, 50% respectively). Changes in Kidney parameters were noticeably reduced. Lipase activity and creatinine decreased dramatically (56%, 77% respectively). Besides insulin level increased 10% compared to 17% reduction in glucose. Lipid parameters were also changed in the treated animals. Reduction in cholesterol (20%), triglycerides (30%), LDL (23%) whereas HDL increased 14%. The ROW for liver and heart reduced significantly. In conclusion, oral treatment with 400mg/kg of the ethanolic extract of areal parts of *C. azarolus* did not show a significant effect on the functional parameters and markers of liver enzymes, kidney and serum biochemical components, however lipid profile indices were improved.

Keywords: *Crateagus azarolus*, liver, kidney, lipid profile and Wistar rats.

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INTRODUCTION

Over the past 10 years, medicinal plants have gained attention due to their potential to heal a variety of illnesses, from everyday illnesses to more serious and chronic situations. Traditional medicine relies on the healing powers of derived syrup from medicinal plants, or even plant components that have been boiled, soaked, choked, or eaten. (Taylor *et al.,* 2001), (Lev and Amar, 2002), (Aburjai *et al.,* 2007), (Hudaib *et al.,* 2008), (Abdelhalim *et al.,* 2017) and (Almuhur, 2019).

Almost 280 species of the Rosaceae family, which includes the common name "hawthorn," are found in East Asia, Europe, and eastern North America (Chang *et al.,* 2002). Globally, more than 20 species of the Crataegus genus are still regarded as useful sources of herbal medicine or pharmaceuticals (Chang *et al.,* 2002). Numerous phytochemical substances found in the plant have led to investigations on its possible medical benefits, which include impacts on the neurological, endocrine and cardio-stimulant systems as well as morbigenous bacteria (Said *et al.,* 2002, Khalil *et al.,* 2008; Beigmohamadi and Rahmani, 2011, Li *et al.,* 2023). A limited number of phytochemical research on *C. azarolus* have reported the presence of flavonoids in Tunisia species and volatile oils in Algerian species, which are examples of active polyphenol components (Lakache *et al.,* 2014; Amina *et al.,* 2018).

A total of 253 phytochemical compositions comprising triterpenoids, lignans, phenylpropanoids, flavonoids and their glycosides, among other chemicals, have been isolated and identified from the C. pinnatifida fruit, leaf, and seed samples. The various pharmacological characteristics of B-type procyanidins, epicatechin, chlorogenic acid, vitexin, hyperoside, procyanidin C1, and rutin have led to their classification as biologically active components (Li *et al.,* 2023).

Crateagus species that were studied in Jordan showed promise for lowering cholesterol and treating diabetes. Al-Mustafa and Al-Thunibat, 2008; Almomani and Sammour 2022; Al-Mazaideh *et al.,* 2022; Al-Mobideen *et al.,* 2022; Altiti *et al.,* 2023) have all reported that leaves, fruit and stems possess antioxidant and antibacterial qualities.

Despite being widely produced and utilized, this species' potential for toxicity has not been thoroughly examined in

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many papers. This is the first study conducted in Jordan to examine the kidney and liver function indices in male Wister albino rats exposed to *Crateagus azarolus* ethanolic areal extract. Additionally, the study aims to assess the harmful effects of plant ingestion on serum biochemical, body weight and organ weight changes.

MATERIALS AND METHODS

Plant extraction

In the spring of 2021, the areal parts (the stem and leaves) of *Crateagus azarolus* were harvested from Ajloun. At Yarmouk University, Dr. Jameel Allahaam classified the plant. The Al al-Bayt University herbarium has a sample (number 3545). The published protocol by Khaleel and Haddadin (2013) was adhered to in the preparation of the ethanol extract. Dried aerial parts were soaked in 75% ethanol solvent for 24 hrs, dried in rotary evaporeter, filtered and kept in fridge for later use.

Experimental animals and dosing

Twelve 200-250g Wister albino rats were acquired from Yarmouk University's Animal House of the Biological Sciences in Jordan and splitted into Two groups of six rats each One group was administered 0.5ml of C. azarolus ethanolic extract (400mg/kg) orally, while the other group was given normal saline as a control. The course of treatment lasted for fourteen days consecutively (Bannoth *et al.,* 2015).

Body and organs weights

The body weight and relative organ weight (ROW) change percentage were assessed using the formulas below based on Ifeanacho *et al.,* (2017)

- Percentage of body weight change = ((total difference in body weight (per group)) /n) × 100.
- Relative organ weight (ROW) = (organ weight (g)/body weight (g)) × 100

Blood sampling and analysis of the biochemical components in the serum

Rats were killed by cervical dislocation at the end of the two-week treatment period. Collected blood in a wax-embedded tube, was centrifuged for 10 minutes at 5000 rpm and the serum was stored frozen for further examination. For the purpose of performing a biochemical examination on serum, kidney and liver components, commercial diagnostic kits were purchased from Biosystems S.A. Costa Brava, Barcelona, Spain.

The following parameters were measured in the collected serum: (a) lactate dehydrogenase (LDH), alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and uric acid and urea; (b) kidney function; creatinine, total bilirubin, total protein, uric acid and urea; (c) glucose and lipid profile; glucose, insulin, cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), glucose and lipase activity).

ETHICAL APPROVAL

Animal experiments at Al al-Bayt University, Mafraq, Jordan, of biological studies follow edapproved protocols of the Animal Ethics Committee (aabu-biology- 2020/11).

STATISTICAL ANALYSIS

The two-way t-test was used to examine the data from the experimental portion (SPSS 2013). The data was displayed as the means (n = 6) ± SD. $P<0.05$ values were taken into consideration for statistical significance.

RESULTS

In this study, biochemical assessment of liver and kidney indices, serum lipid profile and organ weight indices indicated that, the extract exerted significant effect on ALP, ALT and AST enzymes. ALP level dropped (27%) in treated group whereas AST and ALT sharpely rose up to 58%. Total bilirubin decreased significantly (50%), whereas the extract effect on direct bilirubin and LDH level was negligible (table 1). The extract effect on renal function resulted in lower levels of urea (20%), uric acid (17%) while creatinine concentration decreased significantly (77%) when compared to the control group. Total protein, however, was not considerably impacted (table 2).

Two week exposure to the extract caused a substantial effect of the extract on serum glucose and insulin levels, with a 17% drop in glucose and a 10% increase in insulin level (table 3). Interestingly, the extract had a noticeble effect on various lipid parameters (table 4); reduction in cholesterol (20%), LDL (23%) and increasing in HDL levels (14%). The extract also had a significant reduction effect on triglyceride (38%) and lipase activity (56%). Beside that the extract displayed a substantial change on body weight and relative organ indices (ROI) as illustrated in table 5. Body weight was increased 4 folds over the control. And the ROI of liver and heart decreased significantly (25% and 33% respectively), whereas kidney index was not modified pointedly.

DISCUSSION

Numerous reports highlighted the importance of medicinal plants that are often utilized in daily life or during illness to heal various conditions (Almuhur, 2019). According to Lev and Amar (2002), traditional herbs are a good source of a wide range of biological components and bioactive chemicals.

Table 1: The effect of *Crateagus azorolus* extract on the liver enzymes and function parameters

	Control	Crateagus	Effect %
ALP (U/L)	223.0±40.7	180.0±21.63*	27
ALT (U/L)	33.0±7.5	52.0±9.5*	58
AST (U/L)	141.0±19.1	221.00±31.5*	57
LDH (U/L)	145.3±12.8	133.00±11.5	8
Direct bilirubin (mg/dl)	0.10±0.0	0.10±0.0	0
Total bilirubin (mg/dl)	0.2±0.0	0.1±0.0 *	50

Values were reported as mean ± SD (n=6 replicates). Lactate dehydrogenase (LDH), alkaline phosphatase (ALP), aspartate aminotransferase AST, alanine transaminase ALT Asterisk (*) indicates a statistical significance (P<0.05).

Table 2: Effects of the extract on the kidney function parameters

	Control	Crateagus	Effect %
Creatinine (mg/dl)	1.01±0.7	0.23±0.02*	77
Urea (mg/dl)	19.3±2.1	15.33±1.1	20
Uric acid (mg/dl)	2.3±0.2	1.94±0.35	17
Protein (g/dl)	7.6±0.5	8.1±0.57	6

Values were reported as mean ± SD (n=6). Asterisk (*) indicates a statistical significance (P<0.05).

Table 3: Serum glucose and insulin levels in control and Crateagus treated rats (non-fasting)

	Control	Crateagus	Effect %
Glucose (mg/dl)	148.8±6.5	123.0±10.8	17
Insulin (ulU/mL)	0.69±0.01	0.76±0.01*	10

Values were reported as mean ± SD (n=6). Asterisk (*) indicates a statistical significance (P<0.05).

Table 4: Effect of *C. azorolus* on lipid profile

	Control	Crateagus	Effect %
Cholestrol (mg/dl)	51.0±2.0	41.0±7.45	20
Triglyceride (mg/dl)	66.0±4.5	41.33±7.1*	38
LDL (mg/dl)	55.8±3.8	42.3±3.9	23
HDL (mg/dl)	35.8±5.3	40.9±4.6	14
Lipase activity (U/L)	15.8±8.2	7.10±0.58	56

Values were reported as mean ± SD (n=6). Asterisk (*) indicates a statistical significance (P<0.05). High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL)

Table 5: Change in body weight and relative organ weight.

	Control mean ± SD, (n=6)	Crateagus mean ± SD, (n=6)	Effect %
Change in body weight	3.2±1.8	15.6±1.6 *	400
Relative kidney index	0.86±0.53	0.76±0.62	11
Relative Liver index	4.089±0.34	2.985±0.30 *	25
Relative Heart index	0.484±0.05	0.326±0.06*	33

(*P<0.05)

Nonetheless, it has been noted that some medicinal herbs have extremely harmful effects (Nuhu and Aliyu, 2008; Herrine, 2018). This study was created to evaluate the disease (Nazir *et al.,* 2013). Damage poisonous potentials for exposure to *C. azarolus* ethanolic extract on serum biochemical indices, liver and kidney functional indicators and male Wistar albino rats due to the lack of toxic bioactivity of the Jordanian *C. azarolus*.

The liver is an essential organ in the human body that regulates protein, lipid and carbohydrate metabolism in addition to producing bile (Ahsan *et al.,* 2009; Rayese *et al.,* 2013). It also plays a critical role in maintaining body homeostasis. According to reports, hepatic necrosis is subsequently linked to alterations in liver function. The substantial increase in hepatic biochemical markers "like transaminases (ALT & AST), alkaline phosphatase

(ALP), bilirubin, triglycerides and cholesterol" (Kathak *et al.,* 2022) is suggestive of liver to the hepatocyte membrane causes hepatic markers to leak. In this study, rats treated with 400mg/kg Crateagus ethanolic extract showed a significant increase in AST and ALT (58% & 57%, respectively). According to reports, AST and ALT are present in striated muscle tissue in addition to the kidney and testes and ALT is a crucial marker for hepatic injury because the other enzymes are widely distributed in various tissues and organs (Limdi and Hyde, 2023), implying that abnormalities in tissues other than the liver could be the cause of the shift in AST in the serum after Crateagus therapy. In Algeria, total protein increased considerably when administered with a combination of 100 and 200 mg/kg of methanolic *C. azarolus* extract and 100 mg/kg of vitamin C, as compared to the control group that received 100 mg/kg of vitamin C. This suggests that the mixture plays a role in enhancing protein synthesis (Bouaziz *et al.,* 2016).

Because the protein levels in the Crateagus treatment group in this study were not different from those in the control group, it is possible that the phytochemical and bioactive components found in the Jordanian species differ from those grown in Algeria, and as a result, their potential activities and targeted cells and tissues differ. A frequent measure of liver function is bilirubin; a rise in total and conjugated bilirubin value indicates liver damage (Thapa and Walia, 2007), as does a higher rate of red blood cell breakdown (Baranano *et al.,* 2002).The compared group's total bilirubin showed 50% decrease after receiving 400mg/kg of ethanolic Crateagus extract; however, the control group's direct bilirubin remained unchanged from its normal level. Similarly, Wistar rats given 400mg/kg of ethanolic Z. spina-cristia leaf extract demonstrated no change in direct bilirubin, while total bilirubin increased significantly (Khaleel *et al.,* 2021).

Major indicators of renal function include urea, uric acid, and creatinine, which are formed after protein metabolism. According to Renugadevi and Prabu (2009) and Mehrdad *et al.* (2011), their elevated level is suggestive of potential renal failure or renale dysfunction. When ethanolic extract of C. azarolus was administered for two weeks, the levels of creatinine decreased dramatically (77%), but urea, uric acid and total protein did not alter significantly from the control group. The liver produces creatinine, which is transported to the skeletal muscles via the bloodstream (Wurochekke *et al.,* 2008). Serum creatinine levels that are low could be a sign of kidney damage from extract interfering with creatinine metabolism and excretion (Pendota *et al.,* 2009). The remaining kidney functional measurements, however, suggested that the *C. azarolus* extract had no adverse effects on the kidney functional parameters because their values were around ranges observed in a comparable control group.

The lipid profile markers have been enhanced by *C. azarolus* extract, based on glucose and lipid profile study. In addition to a large increase in serum insulin (10%), the Crateagus-treated rats showed a significant reduction in their triglyceride levels (30%) and lipase levels (56%), besides, shown decrease in cholesterol (20%) and LDL (23%) was recorded. According to Ahmadvand *et al.,* (2012), as insulin regulates these processes, lower lipid profile components may arise from suppression of intestinal lipid absorption, a decrease in lipolysis rate, or a decrease in the activity of the enzymes that produce cholesterol.

While the liver and heart organ indices of Wistar rats treated with 400mg/kg of Crateagus ethanolic extract for two weeks showed a substantial ($P<0.05$) drop, however, the rats' body weight increased four times control. According to Alebachew *et al.,* (2014), this might be caused by the bioactive compounds in the ethanolic extract of Crateagus having unfavorable properties, and a possible role in slowing-down metabolism shown as decreased lipase activity, or suppressed intestinl absorption.

CONCLUSION

In final analysis, male Wistar albino rats were used in this work to examine the possible harmful effects of an ethanolic areal extract of *Crataegus azarolus*. According to the findings, kidney functional indicators, liver enzymes, and serum biochemical indices did not significantly change after receiving 400mg/kg of the extract for two weeks. Additionally, the extract showed favorable effects on the lipid profile, such as a notable increase in serum insulin and a decrease in triglyceride levels.

Additional histological investigation could provide a deeper understanding of the alterations observed in the liver and cardiac organ indices in rats treated with Crateagus. Further research to assess Crateagus extract toxicity profile should be conducted, to prevent adverse effects related to its consumption. The study of its acute toxic potentials through assessment of its oral lethal dose (LD_{50}), beside to its chronic consequences based on biochemical, hematological and histopathological studies, will give better understanding of its safe use.

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