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The Paracetamol overdose and Sesame oil protective role against hepatotoxicity and some physiological parameters

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الدور الوقائي لزيت السمسم ضد السمية الكبدية الناتجة عن جرعة زائدة من الباراسيتامول وتأثيراتها على بعض المعايير الفسيولوجية

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Abstract:
The study dealt with the protective effects of sesame oil against paracetamol-induced toxicity in male rabbits. Paracetamol administration resulted in hepatotoxicity, evidenced by increased serum levels of bilirubin, ALT, AST, and LDH, alongside a depression in total protein and albumin. It also induced hematological disturbances, characterized by a significant decrease in red blood cells and hemoglobin and an increase in white blood cells. Co-treatment with sesame oil significantly mitigated these toxic effects, normalizing red blood cell and hemoglobin levels and markedly reducing the elevation in liver enzymes and bilirubin, although these levels of total protein remained significantly different from the control. The white blood cell count was also reduced but not fully normalized. The results demonstrate that sesame oil provides significant hepatoprotective and hematoprotective benefits against paracetamol toxicity.

Keywords: Liver enzymes, paracetamol, red blood cells, sesame oil, white blood cells.

الملخص
تناولت الدراسة التأثيرات الوقائية لزيت السمسم ضد السمية الناتجة عن الباراسيتامول في ذكور الأرانب. وقد أدى إعطاء الباراسيتامول إلى حدوث تسمم كبدي، تجلّى في ارتفاع مستويات البيليروبين، وإنزيمات ALT وAST وLDH في مصل الدم، إلى جانب انخفاض في البروتين الكلي والألبومين. كما تسبب الباراسيتامول في اضطرابات دموية، تمثلت في انخفاض ملحوظ في عدد كريات الدم الحمراء ومستويات الهيموغلوبين، وارتفاع في عدد كريات الدم البيضاء. أدى العلاج المشترك مع زيت السمسم إلى التخفيف بشكل ملحوظ من هذه التأثيرات السامة، حيث ساهم في تطبيع مستويات كريات الدم الحمراء والهيموغلوبين، وتقليل الارتفاع في إنزيمات الكبد والبيليروبين بشكل كبير، رغم أن مستويات البروتين الكلي بقيت مختلفة بشكل ملحوظ عن مجموعة الضبط. كما انخفض عدد كريات الدم البيضاء، لكن لم يعد إلى مستواه الطبيعي بالكامل وأظهرت النتائج أن لزيت السمسم فوائد وقائية كبيرة للكبد والدم ضد سمية الباراسيتامول.

الكلمات المفتاحية: إنزيمات الكبد، باراسيتامول، كرات الدم الحمراء، كرات الدم البيضاء، زيت السمسم.

Introduction

For more than 140 years, oral paracetamol formulations have been used, and at acceptable dosages (up to 4 g per day), they usually don't cause any serious side effects. [1]. However, long-term observational studies have shown that paracetamol therapy, especially at higher doses, is linked to an increase in adverse events related to the kidneys, gastrointestinal tract, and heart. Acute liver failure brought on by inadvertent or accidental paracetamol overdoses has also been documented[2]. With an estimated incidence of 1 per million annually, acute liver failure is extremely uncommon, however it is on the decline [3]. Acute liver failure is rare, but because it affects every organ system, it is of great interest to many different medical specialties[3].

A number of theories have been put out to explain how a paracetamol overdose can result in liver failure and damage [4]. At therapeutic dosages, the liver mainly metabolizes paracetamol via glucuronidation (50–60%) and sulfonation (25–30%), with cytochrome P450 2E1 oxidizing less than 10% of the drug. Small amounts of the hazardous metabolite N-acetyl-p-benzoquinone (NAPQI), which is typically detoxified via glutathione conjugation, are produced by this oxidation [5].Excess NAPQI is produced when sulfate availability and/or sulfotransferase activity are low, or when paracetamol overdose occurs [6]. When this excess attaches itself to mitochondrial proteins, it forms cytotoxic adducts that cause severe hepatocellular necrosis and mitochondrial malfunction [5].

Sesamum indicum L For thousands of years, sesamum indicum L. has been a mainstay in traditional Asian diets due to its high nutritional content and health-promoting qualities. About 20% of the seeds include protein, and they are very high in oil, which makes up around 50% of their content. Because of its high oil content, sesame oil is a popular option for cooking and food preparation because it is stable.Sesame seeds also include high levels of dietary fiber, phytosterols, polyphenols, flavonoids, and ascorbic acid, making its nutritional profile noteworthy. In particular [7].Sesame oil (SO) has been shown to have hepatoprotective qualities, reducing liver damage brought on by several substances in test mice. [8].

2.Materials and Method

Tested Compounds

In this study, the effect of paracetamol (Pc) with or without sesame oil on the liver and some physiological and hematological parameters of male rabbits was investigated. Paracetamol was purchased from a pharmacy, 500mg/ml (paracetamol) (UK). Sesame oil was purchased from the
public market for medicinal herbs in Al-Bayda city.

Animals and Treatments

Twenty-four male white rabbits weighing 2000 g apiece were purchased from Al-Bayda City's public market. The rabbits were kept in cages of six and fed a commercial diet, with unlimited access to food and water. Following a two-week period of acclimation, the rabbits were split up into four equal groups, each consisting of six animals. The first group was used as the control, followed by the second group receiving only sesame oil, the third group receiving only paracetamol, and the fourth group receiving both paracetamol and sesame oil.

For a month, the rabbits received their individual treatments orally through gavage three times each week. Three times a week, each rabbit was given 5 milliliters per kilogram of body weight of sesame oil and 10 milligrams per kilogram of paracetamol. All of the rabbits were put to sleep with methyl alcohol on the thirty-first day of the study, and blood samples were taken for biochemical examination after they were slaughtered.

Blood biochemical parameters and enzyme activities

Samples were centrifuged at 860 xg for 20 minutes to produce plasma, which was then kept at -20°C until it was needed for analysis. Total protein (TP) was measured in stored plasma samples using the Biuret method in accordance with [11].The method of [12] was used to quantify the concentration of albumin (A).The method of [13] was used to measure the total bilirubin in plasma. The method of [14] was used to measure the activity of plasma aspartate transaminase (AST; EC 2.6.1.1) and alanine transaminase (ALT; EC 2.6.1.2).According to [15], lactate dehydrogenase was measured**.**

Statistical analysis

Data were analyzed according to [16].Statistical significance of the difference in values of control and treated animals was calculated by the F test with 5% significance level. Data fromthe present study were statistically analyzed by using Data analysis and carried out by Minitab software [17].

Results and discussion

The serum levels of albumin, bilirubin, and total protein in male rabbits are shown in Table 1. Total protein and albumin levels significantly decreased after paracetamol administration when compared to the control group. Nevertheless, total protein and albumin levels considerably rose when paracetamol and sesame oil were given together, even if they were still lower than in the control group. Additionally, following paracetamol treatment, bilirubin levels increased noticeably. Bilirubin levels, on the other hand, dramatically dropped when paracetamol and sesame oil were mixed as opposed to when paracetamol was used alone.

Table 1. mean ±SE of serum biochemistry of male rabbits treated with paracetamol and a combination of paracetamol (Pc) and sesame oil (So)

Parameter	Control	So	Pc	Pc +So
T. protein	52.2^{a}±1.98	50.6^{a}± 0.42	39.2^{b}±1.05	43.3^{c}±0.77
Albumin	41.3^{a}±0.61	40.4^{a}±1.2	32.3^{b}±0.90	35.3^{b}±0.55
Bilirubin	0.75^{a}±0.01	0.72^{a}±.01	1.3^{b}±0.11	1.0^{b}±0.03

Values are expressed as means ±SE. Mean values within arrow not sharing a common superscript letter were significantly different (P<0.05).

Table 2 shows levels of ALT and LDH. ALT, AST, and LDH increased significantly in the serum of male rabbits after treatment with paracetamol. Levels of ALT, AST, and LDH were alleviated but less than the control after treatment with the combination of paracetamoland sesame oil.

Table 2. Alanine transaminase, aspartate transaminase(AST), and LDH in the serum of male rabbits treated with paracetamol (Pc) and a combination of paracetamol and sesame oil (Pc+So)

parameter	control	So	Pc	Pc+So
ALT	48.0^{a}±1.0	49.7^{b}±0.76	84.1^{b}±2.7	56.1^{c}±0.09
AST	21^{c}±0.70	19.7^{c}±0.49	58.4^{a}±1.2	48.6^{b}±1.2
LDH	724.2^{c}±3.6	729.2^{c}±1.28	927.2^{a}±4.8	815^{b}±5.3

Values are expressed as means ±SE. Mean values within arrow not sharing a common superscript letter were significantly different (P<0.05).

Table 3 displays Treatment with paracetamol had a significant impact on hemoglobin, white blood cell, and red blood cell levels in male rabbits. In particular, after taking paracetamol, hemoglobin and red blood cell counts significantly dropped. These levels, however, reverted to normal when paracetamol and sesame oil were combined, and there was no discernible difference from the control group.
On the other hand, following paracetamol treatment, white blood cell counts dramatically increased. Even while these levels dropped following the sesame oil combo therapy, they were still substantially different from those in the control group. This implies that sesame oil does not fully restore normal white blood cell counts, even though it may lessen some of the hematological effects of paracetamol.

Table 3.The Levels of red blood cells, hemoglobin, and white blood cells of male rabbits treated with paracetamol (pc) and a combination of paracetamol and sesame oil (Pc+So)

Parameter	Control	So	Pc	Pc+So
Red blood cells	6.6^{b}±0.19	6.5^{b}±0.13	5.4^{a}±0.16	5.8^{a}±0.01
White blood cells	7.4^{b}±0.28	7.0^{b}±0.17	9.7^{c}±0.25	8.0^{a}±0.16
Haemoglobin	14.3^{b}±0.48	13.5^{b}±0.34	11.9^{a}±.43	12.5^{a}±0.29

Values are expressed as means ±SE. Mean values within arrow not sharing a common superscript letter were significantly different (P<0.05).

After taking paracetamol, our study found that total protein and albumin levels significantly decreased. Necrosis, which lowers the amount of liver cells involved in protein synthesis, could be the cause of the noticeable drop in total protein [18].The bulk of α and β globulins, albumin, fibrinogen, and other coagulation factors are synthesized by parenchymal cells in the liver, which is the main source of most serum proteins. To evaluate the toxicological consequences of different substances, routine protein testing is carried out [19].

The protein in plasma with the greatest quantitative significance is albumin. Acute inflammation causes increased vascular permeability, which releases it into intercellular spaces and lowers its concentration. Poor liver function, which suggests liver disease, is indicated by low serum albumin levels. Additionally, albumin binds to substances or medications to facilitate their transportation [19].According to [18], a decrease in the liver cells that produce albumin owing to necrosis may be the cause of the observed drop in albumin levels brought on by paracetamol. Increased levels of total protein and albumin in the combination group further supported our findings that sesame oil lessened the harmful effects of paracetamol. When taken as directed, paracetamol is regarded as one of the safest non-steroidal analgesics and antipyretics. However, whether from acute overdose or chronic low dosages, sustained use can result in severe liver necrosis [20].Consistent with earlier findings, there was a significant increase in ALT and AST levels in groups treated with paracetamol in terms of serum biochemical indicators linked to liver function [21]. Functional liver injury is confirmed by elevated levels of these enzymes [22, 23, 24].Prior research [25] linked these alterations to the production of large quantities of N-acetyl-p-benzoquinone imine, an acetaminophen metabolite that is a primary contributor to centrilobular hepatic necrosis and hepatocellular destruction.

Following the use of chemicals or medications such as paracetamol, the serum contains a variety of enzymes that do not originate from extracellular fluid. Some of these enzymes seep into the serum as a result of increased membrane permeability after tissue injury.

A useful method for clinical diagnosis is to measure the activity of blood enzymes such lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Calculating these enzyme activity in bodily fluids aids in forecasting the degree of tissue damage or toxicity caused by a chemical molecule [26].

Hepatocellular injury is frequently detected by the biochemical markers ALT and AST [27].These enzymes are sensitive markers of hepatocellular injury that enter the circulation in hepatocyte necrosis cases. LDH catalyzes the transformation of lactate into pyruvate and is present in the liver, kidneys, skeletal muscles, and platelets. The degree of cell death and harmful effects in tissues high in this enzyme are reflected in elevated LDH levels in human serum. According to our findings, animals given paracetamol had considerably higher levels of ALT, AST, and LDH activities than the control group. These alterations show that paracetamol damaged the liver by rupturing the cell membranes' ability to function normally, which resulted in the serum's release of these enzymes. These results are consistent with research by. [28,29].

Total bilirubin levels significantly increased, most likely as a result of excessive triglyceride release [30].In line with results from [31], the combo group's bilirubin levels dropped after receiving sesame oil treatment. Sesame oil demonstrated its preventive function by lessening the harmful effects of paracetamol. These findings concur with [29, 32].which discovered that treating with sesame oil reduced the harmful effects of CCL4 and markedly raised albumin and total protein while lowering ALT, LDH, and AST levels.

Increased liver function enzymes and abnormal alterations in liver tissue are signs of inflammation [33] and liver damage brought on by acetaminophen (APAP) metabolism, which also causes inflammatory cell infiltration and over expression of inflammatory cytokines (such as IL-1β and IL-6). Furthermore, the pathophysiology of APAP-induced liver damage involves pro-inflammatory cytokines such as IL-1β and IL-6 [34]. Four to twenty-four hours following an APAP overdose, these cytokines are produced [35].Therefore, APAP-induced liver damage may be further reduced by blocking the release of IL-1β and IL-6. According to our research, sesame oil has anti-inflammatory properties in cases of acute liver damage brought on by APAP since it dramatically reduced the release of these inflammatory cytokines as a result of APAP overdose.

According to the hematological study, rabbits treated with paracetamol showed a marked drop in red blood cell count, which may indicate that mature RBCs were destroyed and erythropoiesis was decreased. These outcomes are consistent with research from [9].This could suggest that paracetamol may prevent the kidneys from producing erythropoietin. After taking paracetamol, hemoglobin levels also dropped, which might have lowered the blood's ability to carry oxygen and the quantity of blood that was able to reach tissues [9]. White blood cell counts in the paracetamol-treated groups were significantly higher than in the control group, which is in line with findings from

[36.37].Leukocytosis can also be brought on by physical or psychological stress, and elevated white blood cell counts are indicative of infection or inflammation [38].

Conclusion

Co-administration of sesame oil significantly attenuated the toxic effects induced by paracetamol. The combination group showed a reversal of the pathological trends, including increased total protein and albumin levels, reduced activities of ALT, AST, LDH, and bilirubin, and a dramatic decrease in the release of inflammatory cytokines. These results demonstrate that sesame oil possesses potent protective, anti-inflammatory, and hepatoprotective properties that effectively mitigate the toxicological and hematological damage caused by paracetamol.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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