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The effect of treatment with fructose on some biochemical and immune variables and the protective roles of rosemary extract against these effects in male rats

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ABSTRACT

The current study aimed to understand the effects of fructose sugar on experimental animals and its impact on blood sugar levels, insulin hormone, insulin sensitivity, as well as its effect on inflammatory proteins including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and signal transducer and activator of transcription 3 (STAT3). Additionally, the study sought to investigate the role of rosemary plant extract. This study was conducted on 15 male rats with an average weight of 180-230 grams and ages of 4-5 months, which were divided into three groups of 5 animals each This study was conducted on 15 male rats with an average weight of 180-230 grams and aged 4-5 months. They were divided into three groups, with 5 rats in each group:

• Group 1: Considered the control group and given water and regular feed.

• Group 2: Treated with 2 g/kg of fructose.

• Group 3: Treated with 2 g/kg of fructose and 50 ml of aqueous rosemary extract.

All groups were orally administered their respective treatments for 30 days.

The results showed a significant increase in sugar levels, insulin, insulin resistance, and inflammatory proteins (TNF-α, IL-6, and STAT3) in the fructose-treated group compared to the control group. In contrast, the group treated with fructose and rosemary extract exhibited a significant reduction in sugar levels, insulin, insulin resistance, and inflammatory proteins. This decrease is attributed to the role of rosemary in mitigating the effects of fructose .

Rosemary might be beneficial in reducing blood sugar levels, enhancing insulin secretion, protecting pancreatic beta cells, and demonstrating inhibitory effects on IL-6, TNF-α, and STAT3.

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1. Introduction

High fructose sucrose (HFCS) contains the simple sugar fructose as a free monosaccharide. It is a typical sweetener that is present in a lot of produced and processed foods and drinks that people consume on a regular basis. The consumption of fructose-sweetened drinks has risen significantly and is strongly linked to metabolic diseases. These diseases, along with systemic inflammation, infections, and harmful effects across generations, are widely associated with the increased intake of fructose (Prado et al.,2023). Excessive intake of free sugars, such as fructose, is a major contributor to obesity and metabolic syndrome globally. (Stricker et al.,2021) It is well-established that eating habits significantly influence the body's metabolism (Clemente et al.,2023) In recent decades, dietary patterns have shifted globally, leading to a significant increase in fructose consumption, particularly through sugar-sweetened beverages (Shi et al.,2024). Clinical, experimental, and epidemiological research has shown that excessive consumption of fructose, beyond the recommended levels, can result in several negative health effects. (Hernández et al., 2022). Higher fructose intake diminishes the sensation of fullness, promoting a positive energy balance, and enhances fat storage, which contributes to the buildup of visceral fat (Obayomi et al.,2024).

Increased arterial blood pressure and blood vessel damage are caused by fructose, which also encourages the accumulation of ectopic fat, especially in the liver and skeletal muscle, which results in insulin resistance, inflammation, and abnormal fat metabolism. (de Lima and others, 2024) Therefore, through a number of different processes, increased fructose consumption is linked to the beginning of a number of heart and metabolic problems, such as cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, obesity, and insulin resistance..

(Baharuddin 2024). A diet rich in fructose can cause inflammation in the colon and pancreas, enhance intestinal permeability, lead to fat accumulation in liver tissue, and increase levels of pro-inflammatory cytokines (Wangal.,2020). It is important to note that fructose plays a crucial role in non-alcoholic fatty liver disease, with both preclinical and clinical research demonstrating a robust correlation between fructose intake and the degree of fibrosis and inflammation. Fructose is also regarded as a risk factor for liver cancer.

The detrimental effects of fructose on the body, especially in the liver, can be explained by the activation of several pro-inflammatory, pro-fibrosis, and pro-tumor signalling pathways (Murielet al., 2021). Obesity and overweight are becoming more common worldwide. According to data from the World Health Organisation (WHO), 39% of adults over the age of 18 were overweight in 2016 and 13% were obese. Furthermore, the proportion of overweight children and adolescents rose sharply from 4% in 1975 to 18.5% in 2016..

alterations in eating patterns, such as the intake of beverages with added sugar, processed foods high in sugar, fat, and refined carbohydrates, along with the adoption of the Western diet and low physical activity, are contributing factors to the growing obesity rates worldwide. (Organization,2018).

Multiple studies provide evidence that excessive fructose consumption can lead to the accumulation of adipose tissue, systemic inflammation, the production of adipokines, increased oxidative stress, and, consequently, insulin resistance in various tissues. (Ziolkowska et al.,2021;Abolghasemi et al.,2020). The body's immune reaction to damage or infection is inflammation, which is essential to innate immunity. The usual clinical signs of pain, swelling, heat, and redness are the outcome of a complex cascade of molecular and cellular signals that alter physiological responses (Mata et al., 2021). The pancreas secretes the hormone insulin, which helps move glucose from the bloodstream into the cells of muscles, fat, and the liver, where it is used for energy (Tak et al.,2024) The pancreas secretes insulin into the bloodstream to help reduce glucose levels and maintain them within normal ranges .When muscle, fat, and liver cells lose their sensitivity to insulin, it becomes harder for them to absorb glucose, leading to the development of insulin resistance. In order to facilitate glucose access into the cells, the pancreas is compelled to create more insulin. (Aedhet al., 2023)

If the pancreas can produce enough insulin to compensate for the cells' reduced responsiveness, glucose levels will stay within a healthy range. However, persistently high blood glucose levels can lead to prediabetes in individuals with insulin resistance or those whose pancreatic beta cells fail to produce sufficient insulin People with genetic predispositions or unhealthy lifestyles are at a higher risk of developing insulin resistance or prediabetes. (Zhu et al.,2024) Obesity is a major risk factor for insulin resistance, type 2 diabetes, and metabolic syndrome because chronic inflammation plays a major role in decreased insulin sensitivity. Increased inflammatory cytokine production sets off a number of signalling pathways that encourage fat cell growth and lead to the development of insulin resistance (Alassaf et al., 2024).The use of plant sources to treat human and animal diseases has gained significant attention in several countries, as the compounds found in plants offer a diverse array of biologically active components that can help address various complications arising from diseases (Aschale et al.،2023) In the modern era, medicinal plants have gained significant interest due to their use in treating chronic diseases and their recognition as a preventive health approach in many developed countries (Aleksic et al.,2014).

The rosemary plant, which belongs to the Lamiaceae family, is one of the most important of these plants. Rosemary grows in the Mediterranean basin and is cultivated in many countries around the world due to its multiple uses, including as a cooking spice and food preservative thanks to its antioxidant properties. It has been used as a medicinal herb for centuries, possessing the ability to resist many diseases and is considered an anti-inflammatory. (Rocha et al., 2015) .Natural and chemical toxins lead to significant negative effects on human health in various ways. In this context, the use of herbal medicines is considered a safe alternative to combat these toxins. The plant rosemary, scientifically known as Rosmarinus officinalis, is known to belong to the Lamiaceae family. Rosemary and its components, such as carnosic acid, rosmarinic acid, and carnosol, have a number of health benefits, including anti-inflammatory, antioxidant, antimutagenic, antibacterial, and antiviral properties, as well as analgesic and neuroprotective effects.(Alavi et al., 2021) . Rosemary (Rosmarinus officinalis) contains alkaloids, phenolic acids, saponins, diterpenes, flavonoids, and essential oils, and has antioxidant, anti-inflammatory, antibacterial, anticancer, neuroprotective, cardioprotective, and hepatoprotective effects. While rosemary is generally considered safe for consumption and topical application, allergic reactions and dermatitis have been reported in some individuals (Ghasemzadeh and Hosseinzadeh, 2024). The purpose of the current study is to investigate how fructose affects blood serum levels of several biochemical variables, such as glucose, insulin, insulin resistance, interleukin-6, and tumour necrosis factor-alpha (TNFα). The study also assesses rosemary extract's defensive properties

2. Method

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2.1. 2.1 Experimental animals:

This study was carried out in the animal house connected to Tikrit University's College of Veterinary Medicine between 2024-10-20 and 2024-11-20. Fifteen male white mice were used in this study. The animals were put in sanitised plastic cages that had been set up beforehand. The required cages were set up, sterilised with 99% ethanol alcohol, and split up into three groups, each of which included five animals of similar weights. Twelve hours of light and water and twelve hours of darkness were among the laboratory conditions to which these animals were subjected. Twenty-three to twenty-five degrees Celsius was the temperature. After making sure the animals were disease-free, they were given two weeks to acclimatise to their new environment. Throughout the experiment, they were regularly fed and provided water.

1- The first group (control group): was given water and food daily for30 days.

2- The second group (fructose sugar FRC Fructose): I gavedose1 ml of Sugar with Distilled water At a concentration of 2 g/km For a period of30One day.

3- The third group (Fructose + Rosemary Extract FRC+ROSY): I gavedose1 ml of Sugar with Distilled water At a concentration of 2 g/kg and a dose of 1 ml of rosemary extract at a concentration of 50 ml For a period of30One day.

2.2 **Drugs used in the experiment:**

Fructose sugar, obtained as a white crystalline powder from the Spanish company Charlie, was dissolved in distilled water. The rats were then administered a dose of 1 ml per rat, at a concentration of 2 g/kg of body weight (Wang et al., 2020).

The rosemary aqueous extract was prepared in the laboratory and dissolved in distilled water. It was then given to the mice at a dosage of 1 ml per mouse, with a concentration of 50 mg/kg of body weight (Abdelhalim et al., 2015).

2.2. Proposed Method

1.2.1 Collection of Blood Samples

The Following the trial, the animals were given no food for a full day. The jugular vein was then severed in order to get blood samples. (Jugular vein) and left in test tubes for half an hour at ambient temperature. The serum was then separated from other components using a centrifuge set to 3000 rpm for 15 minutes. Micropipettes were used to separate the serum, which was then put in Eppendorf tubes and kept in a deep freezer at -80°C until biochemical testing was completed

Glucose concentration was estimated .Glucose using (kit)Produced byBiolabo-France Insulin and insulin resistance using a ready-made research kit produced by Sunlong-China and evaluation of IL-6 protein concentration and TNF-α protein concentration and the concentration of the STAT3 protein using a ready-made research kit produced by Sunlong-China.

5.2 Statistical analysis:

The Statistical Package for the Social Sciences (SPSS) version 20 was used to statistically analyse the study's findings, and the t-test was employed to compare the arithmetic means of the various coefficients. according to Cleophas and Zwinderman (2016), at the probability level ($P \leq 0.05$).

3. Results and Discussion

The results presented in Table 1 indicate a significant increase (P<0.05) in blood sugar levels, insulin, insulin resistance, and inflammatory proteins, including tumor necrosis factor alpha (TNF-α) and interleukin-6 and Signal Transducer and Activator of Transcription 3, as a result of fructose consumption in the second group (FRC) of mice that were dosed with fructose, compared to the control group (CTRL). The FRC+ROSY group showed a significant decrease (P<0.05) in blood sugar, insulin, insulin resistance, and inflammatory proteins, including TNF-α and IL-6 and STAT3, compared to the fructose-only group (FRC). This decrease is attributed to the protective role of rosemary in mitigating the harmful effects of fructose.

Table 1. Effect Fructose (FRC) and fructose + rosemary extract (FRC+ROSY)On the studied indicators in the serum of female mice.

Transactions	Groups	Mean	SD	Mean±SD
sugar mg/dl	CTRL	85.00	2.00	85.0±2.0 c
	FRC	137.75	1.71	137.75±1.71a
	FRC+ROSY	96.50	3.87	96.5±3.87 b
insulin (ng/m3)	CTRL	11.04	0.30	11.04±0.3 c
	FRC	30.82	0.94	30.82±0.94 a
	FRC+ROSY	23.44	3.48	23.44±3.48 b
Resistant (Pg/ml)	CTRL	41.71	2.12	41.71±2.12c
	FRC	188.70	7.75	188.7±7.75 a
	FRC+ROSY	94.00	2.57	94±2.57 b
TNF-α (Pg/ml)	CTRL	144.33	5.57	144.33±5.57 c
	FRC	557.64	31.72	557.64±31.72a
	FRC+ROSY	280.79	20.80	280.79±20.8 b
IL-6 (Pg/ml)	CTRL	89.38	6.43	89.38±6.43 c
	FRC	297.11	34.61	297.11±34.61a
	FRC+ROSY	199.49	17.63	199.49±17.63b
Stat3 (Pg /ml)	CTRL	8.79	0.67	8.79±0.67
	FRC	31.91	1.54	31.91±1.54
	FRC+ROSY	23.39	2.66	23.39±2.66

Based on a group of five mice, the data are shown as the mean ± standard deviation. Significant differences are indicated by the vertical arrangement of the numbers and letters; statistical significance is established at a probability level of less than 0.05 (P<0.05).

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3.1. DISCUSSION

Our findings align with previous research (Asgary et al., 2016), which demonstrated that increased fructose intake leads to elevated glucose and insulin levels, potentially raising the risk of developing type 2 diabetes. A study (Iet al., 2022) also indicated that excessive fructose consumption induces an acute insulin response (Softic,2020), though fructose itself doesn't directly trigger insulin secretion. Instead, it increases insulin content in beta cells (Kyriazis et al., 2012). Obese adolescents exhibit a significant insulin response to fructose, suggesting a possible link between fructose intake and hyperinsulinemia (Elliott et al., 2005). High fructose consumption promotes fat accumulation in the liver, increasing the risk of non-alcoholic fatty liver disease (NAFLD), which impairs liver sensitivity to insulin and leads to insulin resistance (Ziolkowska et al., 2021). Consuming large amounts of fructose disrupts leptin signaling, which promotes overeating and weight gain. Obesity exacerbates insulin resistance (Shapiro et al., 2008). TNF-α is one of the inflammatory cytokines that play a role in the immune response and inflammation. Studies indicate that excessive consumption of fructose, especially from industrial sources like high-fructose corn syrup (HFCS), may lead to increased production of TNF-α in the body. This rise in TNF-α may contribute to chronic inflammation and oxidative stress, which are associated with diseases such as obesity, type 2 diabetes, and cardiovascular diseases (Ferder et al., 2010). Excessive consumption of fructose may lead to insulin resistance, a condition associated with increased levels of TNF-α. Insulin resistance can exacerbate chronic inflammation, leading to increased production of inflammatory cytokines such as TNF-α and IL-6 (Zhang et al., 2017). Inflammatory cytokines such as IL-6, TNF-α, and hs-CRP are associated with insulin resistance and type 2 diabetes, as cytokines inhibit the transcriptional activity and protein expression of many molecules related to insulin signaling and its functions, such as GLUT-4. This inhibition weakens insulin's ability to bind to its receptors and initiate final cellular signaling, leading to insulin resistance (Rotter et al., 2003). A study found that exposing mice to a high-fructose diet stimulates the production of pro-inflammatory cytokines from immune cells, such as IL-6 and TNF-α, which activate STAT3 (Veličković et al., 2019). Fructose increases insulin secretion at high concentrations, which may stimulate pathways such as PI3K/Akt that interact with STAT3 and enhance its activity. (Świderska et al., 2018) Rosemary contains alkaloids, flavonoids, and phenols with biological activity that lower blood sugar levels and have many roles. Rahbardar and Hosseinzadeh, 2020). Rosemary is considered one of the herbaceous plants rich in bioactive compounds, which may contribute to lowering blood sugar levels. Thus, rosemary plays a supportive role in blood sugar management through multiple mechanisms. Shankar et al., 2024)). Rosemary is rich in phenolic compounds, which have been proven to possess numerous health benefits, including anti-hyperglycemic properties. Research indicates that rosemary and its components may enhance insulin secretion and improve glucose metabolism. (Naimi, 2014). Rosemary compounds activate insulin signaling pathways in the body, such as the AMPK pathway, which increases cell sensitivity to insulin and reduces resistance, especially in patients with type 2 diabetes (Elbouny et al., 2025). Results showed that ferulic acid and the flavonoid quercetin affect pancreatic cells, enhancing the proliferation of beta cells and leading to increased insulin secretion. (Gushiken et al., 2016) The results showed a decrease in TNF-α levels in the groups treated with rosemary plant extract, due to the plant's ability to reduce reactive oxygen species (ROS) either through direct interaction with free radicals or indirectly. Additionally, rosemary contains the compounds carnosic acid and carnosol, which act as antioxidants. (Ahmed and Babakir, 2020) The results of the current study are consistent with (Yousef et al., 2020). They indicated that rosemary contributes to lowering interleukin-6 levels. (IL-6) This is due to the presence of biologically active

components in rosemary that possess anti-inflammatory, antibacterial, and antitumor properties, in addition to its antioxidant properties and its ability to control and neutralize oxidizing agents. Therefore, this plant exhibits a capacity similar to that of other drugs (et al., 2019) De Oliveira) the protective role of rosemary and its main compounds against natural and chemical toxins in laboratory and biological studies. The protective effects of rosemary and its components are mainly mediated through various mechanisms such as inhibiting oxidative stress, reducing inflammatory mediators including tumor necrosis factor-alpha (TNF-α), interleukin-6, interleukin-17, cyclooxygenase-2 (COX-2), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), as well as modulating apoptotic signaling pathways and mitogen-activated protein kinase (MAPK) (et al., 2021) Alavi). Scientific research indicates that rosemary extracts contain chemical compounds such as carbohydrates, coumarins, glycosides, and phenols, which may contribute to this effect in reducing inflammation, thereby lowering STAT3 protein levels (Soni and Sosa, 2013).

4. Conclusion

Excessive consumption of fructose may be one of the underlying causes of insulin resistance, metabolic syndrome, type 2 diabetes, oxidative stress, and consequently, increased inflammatory proteins due to inflammation leading to many diseases. Meanwhile, rosemary extract has shown the ability to mitigate the negative effects caused by fructose due to its active compounds that play a role in glucose metabolism and insulin secretion, as well as regulating various pathways through numerous positive mechanisms.

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