Libyan Journal of Ecological & Environmental Sciences and Technology
(LJEEST)

LJEEST
ISSN: 2710-5237
www.srcest.org.ly/jou

http://aif-doi.org/LJEEST/060112

Effect of Coenzyme Q10 Against Metabolic Syndrome Induced by Saccharin in Rats

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ARTICLE INFO

Vol. 6 No. 1 June, 2024
Pages (73- 78)

Article history:
Revised form 07 December 2024
Accepted 31 January 2024

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Keywords:

Saccharin - Coenzyme Q10- metabolic syndrome- rats.

ABSTRACT

Saccharin (Sac) is one of the most widely used by dieters as a noncaloric sweetener and by diabetics as a sugar substitute worldwide. The present study aimed to investigate the effects COQ10 against the effect of saccharin at different doses on metabolic syndrome. Methods: rats were divided into 6 groups (10 rats of each), 1st control group, 2nd treated with COQ10 20 mg /Kg b.wt, 3rd treated with Sac 2g/kg b.wt, 4th treated with Sac 1g/kg b.wt, 5th treated with Sac 2g/kg b.wt plus COQ10 and 6th treated with Sac 1g/kg b.wt plus COQ10. Sac and COQ10 were administered orally for 30 days. Liver and kidney functions tests were performed. Results: Revealed data showed that the Sac at different levels treated groups induced significant (P>0.05) increase in liver function marker of ALT, AST activity in comparison with control. In groups administrated Sac in combination with COQ10 showed significant amelioration in biochemical parameters

تأثير الإنزيم المساعد Q10 على المتلازمة الأيضية المستحث بالسكرين في الجرذان

فايزة اللافي ابوبكر [1] بارقة أبوخزام فرج[2]

السكارين هو بديل السكر الشائع الذي يستخدمه أخصائيو الحميات ومرضى السكر في جميع أنحاء العالم. أرادت هذه الدراسة معرفة كيفية مقارنة تأثير الكوانزيم 10 على متلازمة الثمثيل الغذائي بالسكارين عند جرعات مختلفة. وللقيام بذلك، تم تقسيم الفئران إلى ست مجموعات (10 فئران لكل مجموعة). المجموعة الأولى كانت مجموعة سيطرة، والمجموعة الثانية عولجت بالكوانزيم 10 (20 ملجم/كجم) من وزن الجسم، والمجموعة الثالثة عولجت بالسكارين (2 جم/كجم) من وزن الجسم، أعطيت المجموعة الرابعة سكارين (1 جم / كجم) من وزن الجسم، وأعطيت المجموعة الخامسة سكارين (2 جم / كجم) من وزن الجسم بالإضافة إلى كوانزيم 10، وأعطيت المجموعة السادسة سكارين وكوانزيم 10 عن طريق الفم لمدة 30 يومًا. كما تم إجراء اختبارات وظائف الكبد والكلى. أظهرت البيانات المنشورة أن السكارين عند مستويات مختلفة أحدث زيادة معنوية في نشاط علامات وظائف الكبد ALT وAST مقارنة بمجموعة السيطرة. بالإضافة إلى ذلك، أظهرت المجموعات التي أعطيت السكارين بالتزامن مع الكوانزيم 10 تحسنًا ملحوظًا في المعايير البيوكيميائية.

INTRODUCTION

The rising concern about health and life quality have encouraged societies to exercise, eat healthy food and reduce consumption of food rich in sugar, salt and fat, chronic consumption of sugar-sweetened beverages also has been progressively related with a variety of health outcomes such as obesity, type-2 diabetes, and metabolic syndrome (Swithers *et al.*, 2012 and Swithers, 2013). With increased consumer interest in reducing sugar intake and To reduce the risk of these diseases, food products made with sweeteners rather than sugar have become more common (Amin *et al.*, 2016). These high-intensity sweeteners provide a sweet taste like that of sucrose but are not metabolized in the body, and therefore do not lead to calorie

intake. There are five sweeteners (a spartame, saccharin, sucralose, acesulfame potassium, and neotame) are approved by the U.S. Food and Drug Administration (FDA) (Sylvetsky and Rother, 2016, Erbas *et al.,* 2018). Saccharin is firstly synthesized in 1879. It is a very well-known as an inexpensive substitute for sugar as it is a non-caloric sweetener. The article shows the properties, use,metabolism and various synthesis and reactions of saccharine. Moreover, the toxicological reports explain that saccharin is mostly responsible for the bladder tumors observed in the male rats, the relationship between the consumption of saccharin and bladder cancer is afforded by epidemiological studies.(Mahmood and Al-Juboori, 2020).

Saccharin (1, 1-dioxo-1,2-benzothiazol-3-one), the oldest artificial sweetener, is a non-nutritive, non-caloric intense artificial sweetener, 300-500 times the sweetness of sucrose, but has a slight bitter aftertaste, Sac still the widely used sweetener especially prescribed for the diabetics. But since its discovery, its use has been a matter of controversy due to its tumour promoting abilities in second generations of rats. As a result, saccharin was thought to be unfit for human consumption (Iizuka, 2022). It is heat-stable and thus used in hot beverages, canned vegetables, bakery products and reduced sugar jams (Amin *et al.,* 2016). Sac goes directly through the human digestive system without being digested; has no food energy (Okoduwa *et al.,* 2013). There are different forms of saccharin including sodium saccharin, calcium saccharin, potassium and acid saccharin. Sac is known under the E number (additive code) E954. The accepted daily intake of saccharin is 2.5 mg/kg body wt. (Amin *et al.,* 2016). Concerns with regard to the safety of saccharin are of great public health significance and of great interest to the public, because saccharin is consumed by tens of millions of people, including children and even fetuses (Uçar and Yilmaz, (2015).

Coenzyme Q10 (COQ10) is responsible for the generation of ATP via the oxidative phosphorylation by transferring electrons of the respiratory chain, which exists in the mitochondrial membrane of organisms (Song *et al.,* 2017). COQ10 also revealed as a redox-active, antioxidant lipoprotein compound that is found in the phospholipid bilayer of cell membranes of tissues (Silva, *et al.,* 2022). It is an effective natural antioxidant with a fundamental role in cellular bioenergetics and numerous known health benefits. (COQ10) the only lipid soluble antioxidant synthesized endogenously and is present in all cellular membranes and in blood, both in high- and in low-density lipoproteins (Laredj *et al.,* 2014). It plays an important role in cellular metabolism, participating as an electron carrier in both mitochondrial and extra mitochondrial membranes, and also protects membranes and lipoproteins from protein oxidation and lipid peroxidation (Camacho *et al.,* 2018). The biosynthesis of COQ10 takes place in the mitochondria of the liver, heart, kidneys and muscles, where they require a greater amount of energy for their multiple biological functions (Acosta *et al.,* 2016). Because of its essential function in cellular tissues, COQ10 deficiency is a common disorder in certain pathological conditions due to the process of cellular aging (Song *et al.,* 2017). Meat, fish, nuts, and some oils are the richest nutritional sources of (COQ10), while much lower levels can be found in most dairy products, vegetables, fruits, and cereals. Large variations of (COQ10) content in some foods and food products of different geographical origin have been found (Bentinger *et al.,* 2010 and Pravst *et al.,* 2010).

In the above context, the aim of this study was designed to examine the effects of COQ10 as antioxidant against metabolic dysfunction induces by Sac and to study the biochemical and histological changes in liver and kidney induced by different doses intake of Sac.

Materials and Methods

Animal's Male albino Wister rats weighing 150–180 g were used throughout the experiment. They were obtained from the animal house of Department of Zoology College of Science Sebha University , and were housed for at least one week in the laboratory room before testing under a 12 h alternating light/dark cycle. Animals were fed standard laboratory pellets with water ad libitum. All animal procedures were performed by the Ethics Committee of the National Research Centre, egypt (registration number 17/004) which is by the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and complied with the guidelines from the Canadian Council on Animal Care.

Drugs and **chemicals:**

Saccharin was obtained from Cornell Lab, Al-Maadi, Cairo City, Egypt, as white crystalline powder and was dissolved in distilled water according to (Alsoufi *et al.,* 2017). Coenzyme Q 10 was obtained from arab company for pharmaceuticals and medicinal plants Mepaco-Medifood, Enshas El Raml-Sharkeia-Egypt, M.O.H Reg. No. 895/2012. And was dissolved in corn oil according to (Olama *et al.,* 2018) and given orally every day to the rats at a dose of (20mg/kg) of body weight according to (Bauerova *et al.,* 2010) in groups 4, 5 and 6

Treatments:

Rats (It was obtained from the Animal House/Department of Zoology /Sebha University,and was acclimated for aweek before starting the experiment) were randomly allocated into 6 groups (10 rats/ group in the object recognition test) as follows:

• Group 1: normal control received distilled water as 1ml/100g b.wt.

• Group 2: received 1/10 of saccharin LD50 (2g/kg b.wt).

• Group 3: received 1/20 of saccharin LD50 (1g/kg b.wt).

• Group 4: received COQ10 (20 mg /Kg b.wt).

• Group 5: received 1/10 of saccharin LD50 (2g/kg b.wt) plus COQ10 (20 mg /Kg b.wt).

• Group 6: received 1/20 of saccharin LD50 (1g/kg b.wt) plus COQ10 (20 mg /Kg b.wt).

Rats received each of the distilled water, Sac and COQ 10 via oral cavage every day for 30 days.

Preparation of serum samples for biochemical investigations:

Blood samples were collected after decapitation in clean dry centrifuge tubes. Blood sample were centrifuged at 5000 rmp for 20 minutes at 4 ºC to obtain the serum. Serum were separated and kept at – 20 ºC for the determining the Liver/renal function markers Alanine aminotransferase (ALT) level, Aspartate aminotransferase (AST) level in serum.

Statistical analysis:

The resulted values are expressed as mean±SE Reported data represented means of 8 animals. Statistical analysis was performed by one way analysis of variance (ANOVA) followed by post HOC least significant differences analysis (Duncan) was performed using statistical package for social science (SPSS) for Windows software. (Version: 17). The value of $p<0.05$ was considered statistically significant.

Results and discussion

Serum alanine aminotransferase (ALT) level:

The alanine aminotransferase (ALT) level of the serum in different experimental groups illustrated in Table 1 and Figure 1.

Data revealed no significant change was detected in serum ALT level for COQ10 group as compared to the control group. On the contrary, a significant increase was recorded in serum ALT level in Sac 2g/kg b.wt and Sac 1g/kg b.wt treated groups after one month of treatment.

Moreover, in results of serum ALT level, there was a significant decline in Sac 2g/kg b.wt + COQ10 and Sac 1g/kg b.wt + COQ10 as compared to the saccharin treated groups at different doses (2 and 1 g/kg b.wt). While no significant changes in serum ALT level were recorded in Sac 2g/kg b.wt + COQ10 and Sac 1g/kg b.wt + COQ10 groups as compared to the control group but still COQ10 group near to normal at ($P<0.05$).

Table (1): Showing **serum alanine aminotransferase (ALT) level (u/l) of different treated groups.**

Groups	Mean ± SE	Range	P value
Control	29.41 ± 0.93^{c}	4.039	0.040
COQ10	30.652 ± 1.169^{c}	4.958	
Sac (2g/kg b.wt)	47.322 ± 1.613^{a}	7.829	
Sac (1g/kg b.wt)	38.374 ± 1.428^{b}	6.733	
Sac (2g/kg b.wt) + COQ10 (20mg/kg b.wt)	33.04 ± 1.059^{c}	4.672	
Sac (1g/kg b.wt) + COQ10 (20mg/kg b.wt)	32.38 ± 1.244^{c}	2.539	

a, b, c. means having different superscript letters in the same row differ significantly ($P<0.05$). Sac= Saccharin, COQ10= Coenzyme 10.

Values in each column represent Mean ± SE .

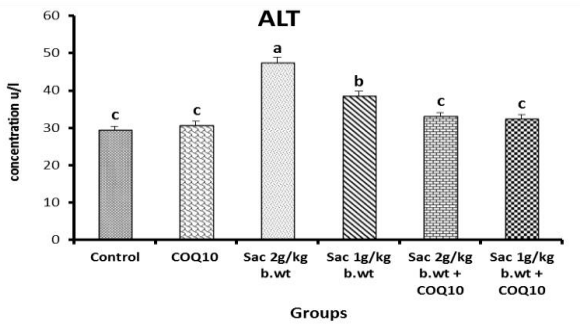

Figure (1): Showing serum alanine aminotransferase (ALT) level of different treated groups, a, b, c. means having different superscript letters in the same row differ significantly ($P<0.05$). Sac= Saccharin, COQ10= Coenzyme 10.

Serum aspartate aminotransferase (AST) level:

Statistical analyses of serum aspartate aminotransferase (AST) level of different experimental groups were illustrated in Table 2 and Figure 2.

We noticed that there was non- significant change in serum ALT level in COQ10 group as compared with the control group. In contrast, there was a significant increase in serum ALT level in saccharin treated groups at different doses (2 and 1 g/kg b.wt) at ($P<0.05$). In addition, it showed a significant recovery of serum ALT level for (Sac 2g/kg b.wt + COQ10 and Sac 1g/kg b.wt + COQ10) groups when compared with low and high dose of saccharin treated groups (2 and 1 g/kg b.wt) but didn't still to the normal at p value ≤ 0.05.

Table (2): Showing serum aspartate aminotransferase (AST) level (u/l) of different treated groups.

Groups	Mean ± SE	Range	P-value
Control	40.286 ± 1.393[d]	6.578	0.000
COQ10	38.772 ± 1.306[d]	4.634	
Sac (2g/kg b.wt)	57.97 ± 1.968[a]	9.018	
Sac (1g/kg b.wt)	54.536 ± 1.891[a]	10.236	
Sac (2g/kg b.wt) + COQ10 (20mg/kg b.wt)	47.976 ± 1.693[b]	4.254	
Sac (1g/kg b.wt) + COQ10 (20mg/kg b.wt)	43.086 ± 1.635[c]	8.288	

a, b, c, d. means having different superscript letters in the same row differ significantly (P<0.05). Sac= Saccharin, COQ10= Coenzyme 10.
Values in each column represent Mean ± SE .

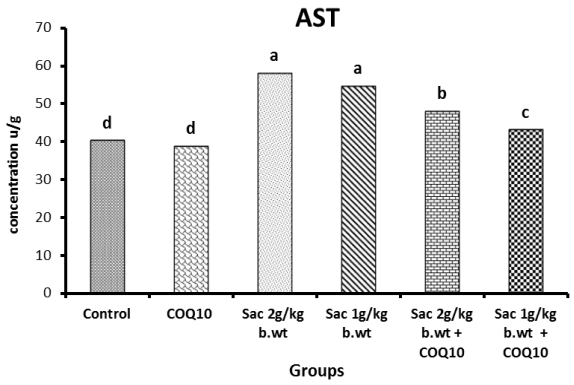

Figure **(24):** Showing serum aspartate aminotransferase (AST) level of different treated groups, a, b, c. means having different superscript letters in the same row differ significantly (P<0.05). Sac= Saccharin, COQ10= Coenzyme 10.

Discussion:

Effect of different doses of saccharin induce metabolic syndrome against COQ10 treatments on liver and kidney functions:

In the current study, there was a significant increase in serum Alanine aminotransferase activity (ALT) Aspartate aminotransferase activity (AST), Urea and Creatinine (Creat) of rat groups administered with different doses of Sac (2 and 1g/kg b.wt) as compared to the control group and a significant decrease was noticed in serum albumin and total protein of rat groups administered Sac at different levels as compared to the control group.

Serum aminotransferases enzymes (ALT and AST) are the most sensitive biomarkers employed in the diagnosis of hepatic damage because these enzymes are cytoplasmic in location and are released into circulation after the cellular damage **(Mcgill, 2016)**. ALT is more specific to the liver and a better parameter for detecting liver damage because AST present in many other tissues like kidneys, heart and testes **(Czuczejko *et al.*, 2019)**.

ALT and AST are hepatocyte cytosolic enzymes; the increased levels of ALT and AST usually indicate liver cell damage and leakage of these enzymes into the main circulation **(Devi and Anuradha, 2010)**. This resulted from cell membrane damage and mitochondrial damage respectively followed by release of more than 80% of total hepatic enzymes from the mitochondria **(Giannini *et al.*, 2005)**. In agreement with the present results, **Amin *et al.* (2016)** demonstrated that low and high doses of saccharin exhibited a significant increase in liver function marker of ALT, AST, ALP activity, total proteins and albumin levels and renal function test (urea and creatinine levels) in comparison with control group. Further, saccharin at high dose induced significant decrease in liver GSH levels, catalase and SOD activity and increase in hepatic MDA level. Overall saccharin harmfully altered biochemical markers in liver and kidney at higher as well as lower doses. That indicate hepatic lesion.

Osfor and Elias, (2003) also reported that saccharin treated rats showed a significant increase in ALT and AST activity after both 6 and 12 weeks of administration. AST levels were significantly higher in saccharine treated group and that chronic saccharin intake reflects various metabolic, hormonal and neural responses in males and females **(Andrejić *et al.*, 2013)**. The elevation in serum aminotransferase activities could be due to drastic effects caused by free radicals interaction with cellular membranes or related to breakdown of liver parenchyma **(Zentella and Muñoz, 2016)**. The changes in liver function could be attributed to hepatocellular impairment which subsequently caused leakage and the release of greater than normal levels of intracellular enzymes into the blood. Elevation in the activities of aminotransferases indicated an early diagnosis of hepatotoxicity and considered as tissue damage biomarkers **(Mcgill, 2016)**.

Saccharin may induce oxidative stress on the liver cells through lowering catalase. **Alkafafy *et al.*, (2015)** demonstrated that saccharin harmfully affects both hepaticctivity and the total antioxidant concentration (TAC) in plasma and renal tissues and alters biochemical markers, not only at high doses, but also at low doses in rats **(Amin *et al.*, 2016)**. In supporting to the present study **Azeez *et al.*, (2019)** exhibited that oral consumption of saccharin at 5 mg/kg and 10 mg/kg can effect on ALT and AST activity, Sac caused increase on ALT and AST activity after 60 days and 120 days of treatment. The changes in liver function could be attributed to hepatocellular impairment. Subsequently, this alteration would cause the release of abnormal

levels of intracellular enzymes into the blood. The elevation in the activity of aminotransferase indicates an early diagnosis of hepatotoxicity and is considered a biomarker of tissue damage **(Amin *et al.*, 2016)**. In addition, **Abdelaziz and Ashour, (2011)** they reported that a low dose of 10 mg/kg. b.w. and a high dose of 500 mg/kg.b.w. of Sac recorded a significant increase in the activity of ALT, AST, and serum markers of liver function. This alteration was suggested as a common sign of impaired liver function **(Amin and AlMuzafar, 2015)**. The elevation in serum aminotransferase activity could be due to an effect caused by free radical interaction with cellular membranes or could be related to breakdown of liver parenchyma **(Muriel, 2009)**.

CONCLUSION

The increase consumption of saccharin plays a crucial role in the detrimental effects on liver and renal function particularly at high doses (Sac 1/10 LD50).

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