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Oxidative Stress in Brain Induced by Artificial Sweetener (Saccharin) and the Possible Influence of the Coenzyme Q 10 in Male Rats.

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A B S T R A C T

Background: Food additives draw in customers, enhance food quality, help people lose weight, and substitute sugar in food—all while having a potentially harmful impact on the health of both adults and children.

Aim: To look into the negative effects of saccharin (Sac) on oxidative stress in brain tissue and determine the protective effects of CoQ10 on brain tissue.

Methods: Six groups of ten rats each were created out of the sixty rats. 1st control group, 2nd treated with 20 mg/kg of CoQ10 b.wt. 3rd treated with Sac 1/10 LD50, 4th treated with Sac 1/20 LD50, 5th treated with Sac 1/10 LD50 plus CoQ10 and 6th treated with Sac 1/20 LD50 plus CoQ10. Sac and CoQ10 were taken orally for a duration of thirty days. Then brain oxidative stress tests were performed.

Results: Saccharin at both low and high dosages showed a notable rise in brain oxidative markers (GSSG, NO and 8OHDG) in contrast to the group under authority. However, in contrast, CoQ10 supplementation reduced brain oxidative markers (GSSG, NO and 8OHDG) compared to Sac groups and nearly recovery in comparison with a control cohort.

Conclusions: It is possible to draw the conclusion that saccharin has negative effects on brain tissue and raises oxidative indicators both at low and high dosages. However, applications of CoQ10 showed reduction in brain oxidative stress markers and protection from oxidative damage.

1 Introduction

Table sugar is not nearly as sweet as artificial sweeteners, which require lower amounts to get the same sweetness. Concerns about health and the quality of life have grown over the past few decades, which has pushed societies to exercise, eat a balanced diet, and consume fewer foods high in sugar, salt, and fat **(Anushkkaran, 2019)**. Food products made with sweeteners instead of sugar, like aspartame, saccharin, acesulfame-K, and cyclamate, have become more popular due to consumer interest in reducing their sugar intake. These sweeteners can replace sucrose as a sugar and are widely used in dairy products, diabetes, and energy control diets worldwide **(Hasan *et al.*, 2023)**.

In 1879, saccharin is first synthesized. It is renowned for being a less expensive to sugar because it is a non-caloric sweetener. is frequently used in soft drinks, baked goods, jams, canned fruit, candies,

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dessert toppings, and chewing gum in addition to being a tabletop sweetener (**Uçar & Yilmaz, 2015).** Since cooking does not lessen saccharin's sweetening, it is a great addition to low-calorie and sugar-free goods (**Azeez *et al.*, 2019)**, in tobacco products as well as in formulas for pharmaceuticals. Saccharin's benefit-risk analysis is hardly noteworthy. Furthermore, epidemiological research provide evidence linking saccharin consumption to bladder cancer, and toxicological findings clarify that saccharin is mostly to blame for the bladder tumors seen in male rats. Saccharin's chemistry of is interesting due to its suspected alleged carcinogenic properties and potential application as metal poisoning antidote. It is now widely acknowledged that oxidative stress and diseases linked to lifestyle choices are closely associated **(Razzak & Al-Juboori, 2020)**. Saccharin's production of oxidative stress may shed light on the sweetener's role in the development of neuro-diseases and carcinomas. This effect is mostly noticed when the bladder, brain, or other tissues store large amounts of sugar. Sac may cause oxidative stress to brain cells by reducing plasma total antioxidant content (TAC) and catalase activity **(Salim, 2017)**. Saccharin has been shown to have detrimental effects on rat brain tissues at both high and low dosages (**Moktar *et al.*, 2021)**.

Coenzyme Q10 (CoQ10) is a widely used co-factor in the human body, operating inside the inner membrane of the mitochondria, where it is necessary for the electron transport chain to produce ATP (adenosine triphosphate) (**Manzar *et al.*, 2020)**. Furthermore, CoQ10 functions as an antioxidant, defending the cell against reactive oxygen species (ROS)-induced oxidative stress and preserving a proton (H+) gradient across lysosome membranes to promote the breakdown of waste products in the cell. As we age, our bodies lose some of their CoQ10, which can lead to a number of systemic symptoms. One effect of CoQ10 shortage at the cellular level is apoptosis, which is visible in central nervous system (CNS) tissues.The kidneys, heart, and brain all have mitochondria where CoQ10 is biosynthesised. In light of the foregoing, the purpose of this investigation was to examine the impact of ingesting saccharin on the brain at progressively higher dosages.

2 Materials and Methods

Male albino animal Throughout the experiment, 150–180 g wiener rats were employed. Before being tested, the animals were kept in a laboratory room with a 12-hour alternating light/dark cycle for at least one week. They were taken from The National Organization of Drug Control and Research's animal house in Dokki, Cairo, Egypt. The animals were given regular lab pellets and unlimited water. The National Research Center's Ethics Committee (registration number 17/004) conducted all animal procedures in accordance with the Canadian Council on Animal Care's guidelines and the National Institutes of Health's Guide for the Care and Use of Laboratory Animals.

Drugs and chemicals:

According to a study by **Amin *et al.* (2016),** sac was purchased as a white crystalline powder from Cornell Lab (Al-Maadi, Cairo City, Egypt) and dissolved in distilled water.According to a study by **Alsoufi *et al.* (2017),** CoQ10 was acquired from the Arab Company for Pharmaceuticals and Medicinal Plants (Mepaco-Medifood, Enshas El Raml, Sharkeia, Egypt; M.O.H Reg. No. 895/2012) and dissolved in maize oil.

Treatments:

For the purpose of evaluating object identification, six groups of ten rats each were randomly assigned. For a duration of thirty days, rats were administered oral gavage with each of the following treatments.

• **Group 1 (G1):** distilled water (1 ml/100 g bw) was given to this normal control group.

• **Group 2 (G2):** CoQ10 (20 mg/kg bw) was administered according to **(Olama *et al.*, 2018)**.

• **Group 3 (G3):** was given 1/10 of saccharin LD50 (2 g/kg bw).

• **Group 4 (G4):** was given 1/20 of saccharin LD50 (1 g/kg bw).

• **Group 5 (G5):** was given CoQ10 (20 mg/kg bw) in addition to 1/10 of saccharin LD50 (2 g/kg bw).

• **Group 6 (G6):** was given 20 mg/kg bw of CoQ10 in addition to 1/20 of saccharin LD50 (1 g/kg bw).

The doses of drugs in (G3, G4, G5 and G6) are received based on (**Moktar *et al.*, 2021)**.

Preparing a brain homogenate for biochemical analysis:

Rats were put to death by being beheaded, and their brains were meticulously removed. Subsequently, the brain tissues were separated and promptly weighed to prevent any potential drying effects, before being

preserved at -80°C. The homogenate was subjected to a cooling centrifuge (2k15; Sigma/Laborzentrifugen) at 4,000 rpm for five minutes. The supernatant obtained from this process was utilized to ascertain the parameters of oxidative stress such as (Glutathione oxidized (GSSG) content), Nitric oxide (NO) and 8-hydroxyl-2-deoxyguanosine (8-OHDG) contents.

Statistical analysis:

The values obtained are presented as mean ± SE. The means from eight animals are included in the reported statistics. One-way analysis of variance was used for the statistical analysis, and post-hoc least significant difference analysis (Duncan) was performed after that. The statistical package for social science on Windows (Version: 17) was used to do the statistical study. When $p < 0.05$, the data was deemed statistically significant.

3 Results

Oxidative stress markers in the Brain tissue:

1- Oxidized glutathione (GSSH) content in brain tissue:

Results of brain GSSH content showed in Table 1 and Figure 1.

Data of brain GSSH content in CoQ10 group exhibited non-significant change in contrast to the group under authority. On the contrary, there was a significant increase in brain GSSH content for saccharin treated groups at different levels (1/10 and 1/20 of LD50) following a month of therapy at ($P<0.05$).

However, there was a significant decline in brain GSSH content for Sac 1/10 LD50 + CoQ10 and Sac 1/20 LD50 + CoQ10 treated groups as compared to the Sac 1/10 LD50 and Sac 1/20 LD50 groups. Whilst, CoQ10 plusminimal dosage didn't show any significant for brain GSSH content in contrast to the control group, although the CoQ10 group is still close to normal. at P<value 0.05.

Table (1): Showing of oxidized glutathione (GSSH) **content in brain, (umole/g tissue) of different treated groups.**

Groups	Mean ± SE	P-value
Control	24.65± 0.687^{e}	000.0
CoQ10	18.74± 0.665^{e}	
Sac 1/10 LD50	65.15± 1.777^{a}	
Sac 1/20 LD50	44.86± 1.432^{b}	
Sac 1/10 LD50 + CoQ10	31.45± 1.054^{c}	
Sac 1/20 LD50 + CoQ10	26.75± 0.706^{d}	

The means that differ significantly ($P<0.05$) in the same column with different superscript letters are a, b, c, d, and e.

Figure (1): showing oxidized glutathione (GSSH) content, (umole/g) of various treatment groups, a, b, c, d, and e. denotes substantially distinct superscript letters in the same row ($P<0.05$).

2- Nitric Oxide (NO) content of brain:

Results of brain NO content of different experimental groups illustrated in Table 2 and Figure 2.

Data of brain NO content revealed any marked change in Group CoQ10 in contrast to the group under authority. Regarding contradiction, there was marked raise in brain NO content for Sac 1/10 LD_{50} and Sac 1/20 LD_{50} treated groups after one month of treatment at ($P<0.05$).

Moreover, it was noticed a significant decrease in brain NO content in Sac 1/10 LD_{50} + CoQ10 and Sac 1/20 LD_{50} + CoQ10 treated groups when compared to the groups given varying degrees of saccharin treatment (1/10 and 1/20 of LD50) after one month of treatment but fell short of the typical level at ($P<0.05$).

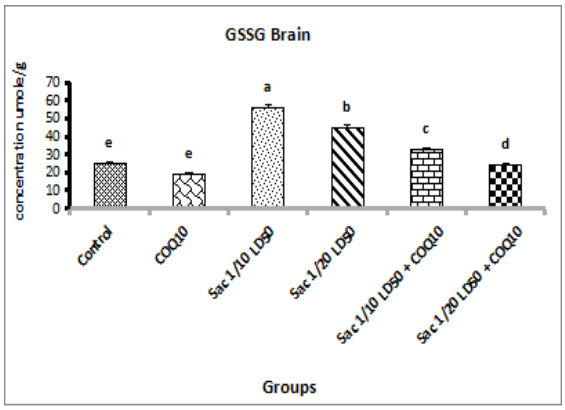

Table (2): Showing of Nitric Oxide (NO) content in brain, (umole/g tissue) of several treatment groups.

Groups	Mean ± SE	P-value
Control	0.33 ± 0.011^{c}	000.0
CoQ10	0.28 ± 0.009^{c}	
Sac 1/10 LD50	0.8 ± 0.025^{a}	
Sac 1/20 LD50	0.74 ± 0.024^{a}	
Sac 1/10 LD50 + CoQ10	0.49 ± 0.016^{b}	
Sac 1/20 LD50 + CoQ10	0.42 ± 0.013^{b}	

The means that differ significantly (P<0.05) in the same row with distinct superscript letters are a, b, c, and d.

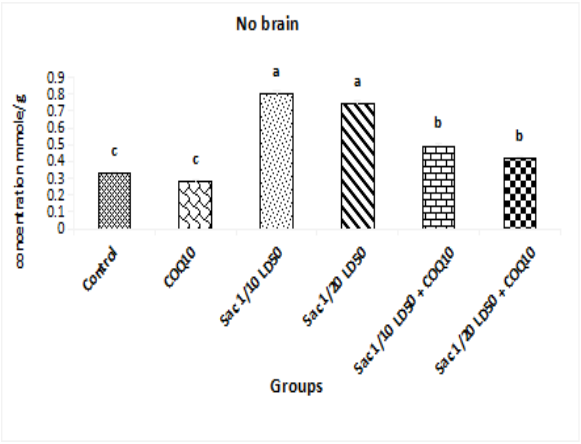

Figure (2): Showing brain Nitric Oxide (NO), **(mmole**/g tissue) of several treatment. The means that differ significantly (P<0.05) in the same row with distinct superscript letters are a, b, c, and d.

3- 8- Hydroxyl-2-deoxyguanosine (8-OHDG) content of brain:

Statistical analysis of brain 8- hydroxyl-2-deoxyguanosine (8-OHDG) contents of different experimental groups are illustrated in Table 3 and Figure 3.

There was a significant decrease in brain 8-OHDG content in CoQ10 group in contrast to the group under authority. Quite the opposite, the groups (Sac 1/10 LD_{50} and Sac 1/20 LD_{50}) recorded a significant increase in brain 8-OHDG content after one month of treatment at (P<0.05).

Whereas, brain 8-OHDG content showed a significant decrease for Sac 1/10 LD_{50} + CoQ10 and Sac 1/20 LD_{50} + CoQ10 treated groups as opposed to those that received varying degrees of saccharin treatment (1/10 and 1/20 of LD50). At the same time, there was any marked change between Sac 1/20 LD_{50} + CoQ10 and control group at P value < 0.05.

Table (3): showing of 8- hydroxyl-2-deoxyguanosine (8-OHDG) content in brain, (pg/g tissue) of different treated groups.

Groups	Mean ± SE	P-value
Control	142.9 ± 4.89^{d}	000.0
CoQ10	133.5 ± 4.63^{e}	
Sac 1/10 LD50	226.3 ± 7.46^{a}	
Sac 1/20 LD50	198.4 ± 6.15^{b}	
Sac 1/10 LD50 + CoQ10	160.8 ± 5.16^{c}	
Sac 1/20 LD50 + CoQ10	153.4 ± 5.24^{cd}	

The means that differ significantly (P<0.05) in the same column with different superscript letters are a, b, c, d, and e.

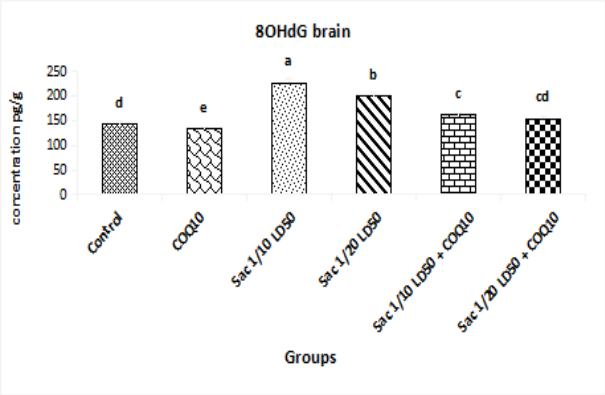

Figure (3): Showing brain (8-OHDG) (pg/g tissue) of several treatment. The means that differ significantly ($P<0.05$) in the same row with distinct superscript letters are a, b, c, and d.

4 Discussion

An imbalance favoring oxidants over antioxidants can lead to oxidative stress, which can potentially harm cells or their constituent parts **(Sharifi-Rad *et al.*, 2020)**. The majority of these oxygen-derived compounds are created at low concentrations by regular aerobic metabolism, and the cell damage they inflict is continually corrected. However, the damage results in ATP depletion under extreme oxidative stress conditions that cause necrosis, prohibiting regulated apoptotic death and damage to DNA (**Pizzino *et al.*, 2017)**. From the present study, it was noticed a significant increase in brain malondialdehyde (MDA) in Saccharin groups at different doses in contrast to the group under authority. In supporting to the current results, **Hasan & Alkass, (2020)** claimed that research on saccharin revealed that it lowered cell respiration in a dose-dependent way and enhanced ROS generation at both basal and peak glucose levels. Saccharin treatment has been demonstrated to significantly suppress the antioxidant defense mechanisms, notably a decrease in catalase, SOD, and GSH activities, preventing damaging radical-induced cell death. (**Amin *et al.*, 2016)**. In contrast, MDA, NO and GSSG levels increased a result of ROS action on cell **(Bouyahya *et al.*, 2021)**.

It's possible that inflammation started by brain cells is what causes the oxidative stress brought on by high saccharin levels. Reactive oxygen species (ROS) such hydrogen peroxide and superoxide anion are released by stimulated inflammatory cells during a respiratory burst **(Amin & AlMuzafar, 2015)**. Peroxynitrite, which is produced when superoxide and nitric oxide (NO) react under regulated conditions, has the ability to oxidize biomolecules in a manner akin to that of the hydroxyl radical **(Martemucci *et al.*, 2022)** . In the same line **Hassan *et al.* (2022)** demonstrated how oxidative stress plays a role in the development of neurodegenerative diseases. In neurodegenerative illnesses, oxidized lipids, proteins, and DNA are accumulated by the neuronal populations most afflicted. Reduced levels of glutathione (GSH), the primary cellular antioxidant that cells use to repair oxidized protein residues and scavenge reactive oxygen species (ROS), are associated with these indicators of oxidative damage. GSH also causes an increase in the concentration of oxidized GSSG.

High saccharin levels have been shown to cause oxidative stress, which is linked to inflammation that starts in the brain cells. Reactive oxygen species (ROS) such hydrogen peroxide and superoxide anion are released by stimulated inflammatory cells during a respiratory burst **(Helal *et al.*, 2019).** PEroxynitrite, which is produced when superoxide and nitric oxide (NO) are carefully combined, can oxidize biomolecules in a way that is comparable to that of the hydroxyl radical **(Radi, 2014).**

Furthermore, various approaches have been used to evaluate oxidative stress in people and animal models. Additionally, DNA bases are very vulnerable to oxidation by reactive oxygen species (ROS) **(Katerji *et al.*, 2019)**. 8-hydroxy-2′-deoxyguanosine is the most observable DNA oxidation product in vivo (8-OHdG). Following its discovery as a sensitive measure of DNA damage, 8-OHdG rose to prominence as a biomarker for aging, degenerative illnesses, and carcinogenesis **(Graille *et al.*, 2020).** In parallel with the present study, **Sharifi-Rad *et al.* (2020)** demonstrated how normal aerobic metabolism produces reactive oxygen species (ROS) at a low level, allowing for ongoing cell damage repair. ROS include free radicals, H2O2, and peroxides, all of which have the potential to cause harm to cells. But high levels of oxidative stress lead to ATP depletion, which stops cells from dying normally, which can damage DNA. The inflammation of the brain cells may be caused by the oxidative stress that high saccharin dosages create **(Azeez *et al.*, 2019)**. In addition to secondary oxidants and DNA-reactive aldehydes, the inflammatory process causes oxidative or nitrosative stress, lipid peroxidation, and excess ROS and RON (superoxide anion and H2O2) **(Gong *et al.*, 2016**).Reduced brain function could be the cause of increased oxidative stress in saccharin-treated groups rather than only an increase in lipid profiles **(Djukanovic *et al.*, 2019).** In the same line **Zhu *et al.***

(2022) observed that the use of artificial sweeteners demonstrated that oxidizing circumstances can result in elevated levels of 8-OHdG, a DNA hydroxylation byproduct. Thus, it has been suggested that 8-OHdG serves as a marker for oxidative damage to DNA both in vivo and in vitro. Comparably, the current investigation concurs with **Song *et al.* (2017),** who found that all groups under investigation that were given varying dosages of saccharin had higher concentrations of 8-OHdG.

On the other hand, the present study noticed that groups treatment with CoQ10 (G2, G5 and G6) showed marked decrease in the previously mentioned oxidative stress parameters (Glutathione oxidized (GSSG) content), nitric oxide (NO) and 8- hydroxyl-2-deoxyguanosine (8-OHDG). When compared with saccharin treatment groups at a different dose (G3 and G4), and a similar level in these markers when compared with the control rats. In agreement with the current study **Al-Kareem *et al.* (2022)** shown that CoQ10 has an antioxidant defense mechanism-based free radical scavenging ability that protects or mitigates the effects of oxidative stress in rat tissue.

Numerous studies have shown that giving CoQ10 to lab animals that were exposed to hazardous substances may aid to keep the body's antioxidant status and antioxidant enzyme levels at normal and decrease oxidative stress markers **(Çolak & Uysal 2017)**. Furthermore, young mice given CoQ10 supplementation showed a considerable rise in the endogenous level of vitamin E in the liver, heart, and plasma, While **Zhang *et al.* (2022)** have demonstrated a neuroprotective effect in brain cell models of oxidative stress, they also imply that the increased antioxidant ability of CoQ10 is partially linked to rising vitamin E levels. **Samimi *et al.* (2019)** demonstration that pre-treating with CoQ10 maintains mitochondrial membrane potential and lowers the production of reactive oxygen species lends credence to the current findings.

In addition, consistent with this possibility, found that CoQ10 supplementation in vitro protected DNA from oxidative damage caused by hydrogen peroxide.

5 Conclusions

Artificial sweeteners such as (Saccharin) offer a few of the health advantages in low concentration.On the other hand, these sweeteners are frequently hazardous in large amounts over time. It has been demonstrated that consuming them can have minor to major negative effects, such as headaches or potentially fatal brain damage. CoQ10 possesses anti-CoQ10 effectively improves degenerative brain disease by improving antioxidant properties in the body and antioxidant properties, allowing it to play a possible therapeutic role.

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