Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

The protective effect of coenzyme Q10 against radiation-induced oral mucositis:An experimental study

Rasha Refaat[1], Nada Sholkamy[2], Enas Alaa Eldin Abd Elaziz[3], Ahmed Mostafa Abdel-Azeez Hassan[4], Ahmed Abdallah Khalil[5]

[1] Teaching Assistant of Oral Medicine, Oral Diagnosis and Periodontology, Faculty of Dentistry, Deraya University, Egypt.
[2] Lecturer of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Minia University, Egypt.
[3] Assistant Professor of Oral and Maxillofacial Pathology, Faculty of Dentistry, Minia University, Egypt.
[4] Lecturer of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Minia University, Egypt.
[5] Professor of Oral Diagnosis and Periodontology, Faculty of Dentistry, Minia University, Egypt.

*Corresponding Author
Rasha Refaat

Article History
Received: 21.08.2025
Revised: 16.09.2025
Accepted: 22.10.2025
Published: 11.11.2025

Abstract: ***Purpose:*** Evaluating the influence of coenzyme Q10 (CoQ10) supplementation as a novel therapeutic strategy in the prevention of radiation-induced oral mucositis (RIOM). ***Methods:*** The study has been conducted on 39 rats; 13 of them served as the control group (group I). The remaining rats have been subjected to radiation exposure of the neck and head region with or without oral administration of CoQ10 (group II and group III) . The oral mucositis index (OMI) was scored, pro-inflammatory markers Tumor Necrosis Factor-alpha (TNF-α)] and interleukin-1 beta (IL-1β) and superoxide dismutase (SOD) were evaluated. ***Results:*** The oral mucositis scores (0–5 points), for radiation-exposed groups significantly increased one and two weeks post-radiation (Group II: 2.8 ± 0.9 and 4.5 ± 0.7; Group III: 1.8 ± 1.4 and 3 ± 2.2), whereas Group I remained scoreless at 0, as proven by Friedman's test $p < 0.001$ $w = 0.526$ and 0.096, respectively. Regarding the hematological assessment, concentrations of Tumor Necrosis Factor-alpha and interleukin-1 beta were significantly the highest in Group II (107.5 ± 2.6 and 63.4 ± 2.6 pg/ml), lower in Group III (92.7 ± 1.3 and 42.8 ± 1.3), and the lowest in Group I (64.2 ± 2.9 and 25.7 ± 0.7) with a high effect size (η^2=0.984, 0.989). The SOD activity presented an opposite variation, as it was greatest in the III (2.87 ± 0.08 µ/ml) and smallest in the II (0.96 ± 0.03), with $\eta^2 = 0.993$. ***Conclusion:*** CoQ10 can ameliorate oral mucositis induced by radiation through its anti-inflammatory and antioxidant effects.

Keywords: Radiotherapy, Oral Mucositis, Coenzyme Q10.

INTRODUCTION

Head and neck cancer (HNC) ranks as the 17th most prevalent disease globally, with about 660,000 novel cases and 325,000 deaths per year.[1] This cancer encompasses several forms, including neck tumours, otolaryngological tumours, and oral-maxillofacial tumours, including nasopharyngeal, hypopharyngeal, oropharyngeal, and laryngeal tumors. Currently, radiation thyrapy has gained prominence as a treatment for HNC cases.[2] Radiation-induced osteonecrosis of the mandible is a significant complication in head and neck cancer cases receiving RT. It jeopardizes treatment tolerance, induces tissue damage, diminishes quality of life, and escalates healthcare resource utilization. [3]RIOM is a detrimental consequence of radiation administered to the head and neck area, significantly diminishing patients' quality of life. Mucosal injury is defined by erythema, oedema, and ulcerations of the oral mucositis. [4] The prevalence of Radiation-induced osteonecrosis of the mandible in head and neck irradiation approaches 100%.[5] The pathophysiology of RIOM encompasses both indirect and direct mechanisms. The direct impact results from DNA strand apoptosis and breakage induced by radiation, leading to a decrease in the regeneration of the basal epithelium. The indirect impact arises from mechanisms like the production of inflammatory mediators, secretion from salivary glands, & neutropenia, leading to the degradation of the oral mucosa.[6] The disruption of equilibrium among oxidative stress, oxidants, and antioxidants is believed to significantly contribute to the pathophysiology of radiation therapy-induced oral mucositis. Regulation of oxidative stress is crucial for the avoidance and management of mucositis.[7] Nonetheless, tactics used to control RIOM continue to operate at institutional and/or individual levels based on internal protocols and professional acumen.[8]

Antioxidant medications are believed to contribute to the prevention and treatment of mucositis.[8] CoQ10, or ubiquinone, is a recognized antioxidant that serves a protective function in several physiological and pathological processes. It is a crucial chemical for electron transport in oxidative phosphorylation and constitutes a significant component of the respiratory chain at the mitochondrial level, functioning inside the mitochondrial membrane, as well as in other cellular membranes, including the plasma membrane and cytoplasm. The antioxidant properties within the mitochondrial electron transport chain augment electron transport efficiency, mitigate uncontrolled electron loss, facilitate the recycling of other antioxidants like vit. E and C, and directly neutralize free radicals and oxidants, thereby diminishing harmful compounds.[7] it is a lipophilic molecule situated on the inner aspect of the mitochondrial membrane. Our research seeks to assess the effectiveness of CoQ10 in preventing radiation-induced oral mucositis in rats.

RESULTS AND OBSERVATIONS:

Ethical regulations:

All studies have been executed in line with the advice and authorization of the local Ethics Committee of the Faculty of Dentistry, Minia University (Approval no 96-742-2023) and according to the internationally accepted principles of the public health service (PHS) policy on human care and utilization of laboratory animals.

Sample Size and Categorization:

Prior to initiating the investigation, the requisite sample size for each group was established by a power calculation based on data derived from a preceding study. [5.9] A sample size of 13 rats per group was established to provide 80% power for the independent samples t-test at a significance concentration of 0.05, utilizing G Power 3.1 9.2 software.

Rats have been randomly assigned to 3 groups: Group I (control group), Group II, which had head and neck radiation with concurrent oral administration of olive oil, and Group III, which got radiation along with oral CoQ10 (Fig. 1).

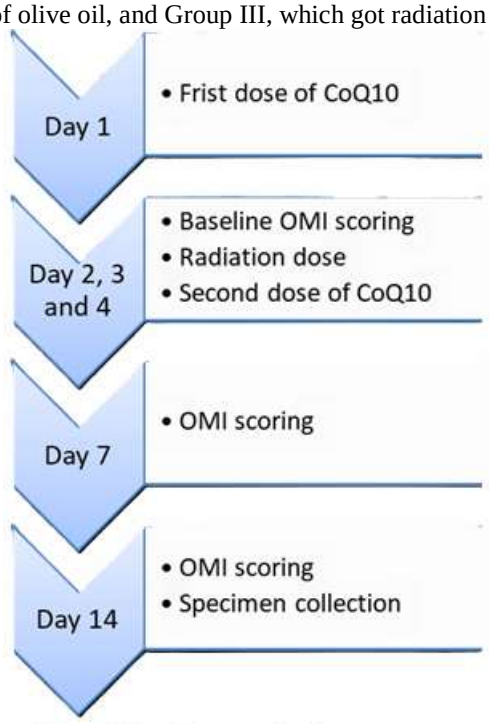

Figure (1): a diagram showing sequence of events for group III

In our investigation, 39 young adult male rats, weighing among 250 and 300 grams, have been kept in the institutional animal facility in clean plastic cages (5 rats per cage) under regulated temperature, adequate ventilation, 55% humidity, and a twelve-hour light/dark cycle. They were permitted to acclimatize for one week prior to the commencement of the studies. The rats have been provided with pellets and given access to potable water.

Group I had thirteen rats (no treatment or radiation administered; negative control group), whereas the experimental groups (Group II and Group III) involved twenty-six rats. In Group II, radiation therapy (15 Gy) has been administered only to the head and neck area, accompanied with oral administration of olive oil at a dosage of 200 milligrams/kilogram. In Group III, the rats received radiation therapy (15 Gy) on the second day of the experiment and were administered 200 milligrams per kilogram of CoQ10 orally once daily from the first to the fourth day of the trial.[10, 11, 12]

Preparation of Coenzyme Q10 (CoQ10)

The CoQ10 solution was prepared by dissolving CoQ10 powder, provided as a gift sample by Mepaco—Arab Co. for Pharmaceuticals & Medicinal, in olive oil. Fresh CoQ10 concentrations have been made shortly previously to delivery and shielded from light prior to being administered to Group III animals. A dosage of 200 milligrams/kilograms was applied in the current investigation. The dose selection was based on prior research indicating that 200 milligrams/kilogram is enough to penetrate the blood-brain barrier and provide neuroprotection. This dosage has shown

beneficial against pathology caused by oxidative stress and inflammation. [13] it was administered once daily for the first four days of the trial. Group II received a placebo consisting of olive oil devoid of CoQ10 (Fig. 2).

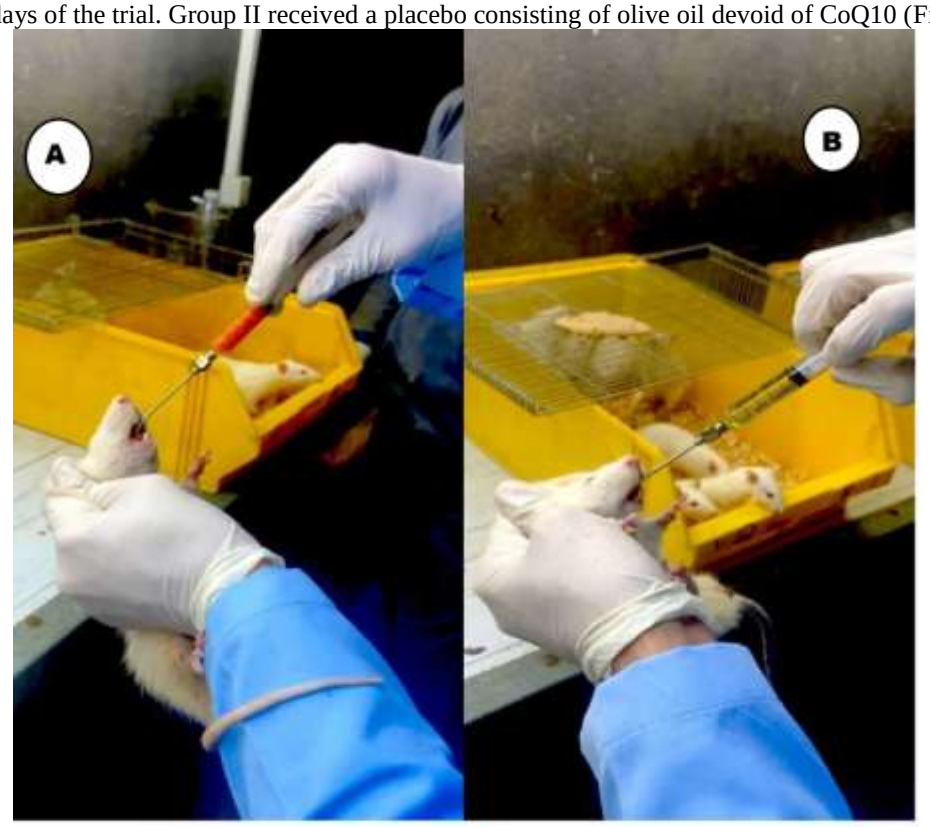

figure (2)
(A) group III : receiving CoQ10 dissolved in olive oil
(B) group II: receiving olive oil

Irradiation of experimental animals:

In the research, radiation therapy (RT) was administered as a single dose of 15 Gy to the animals, which were positioned identically in the apparatus after anesthesia with ketamine/xylazine (80-100 mg/kg IP/10-12.5 mg/kg IP, respectively). 2.0-millimeters aluminium filtration (300-kV peak) at a radiation rate of 1.9 Gy/min with the Elektra Synergy platform at **at Minia Oncology Center** (Fig. 3). The target volume, designed to shield the rat's brain and eyes from radiation therapy effects, was generated using the 3D-conformal radiation therapy approach from two regions. Subsequent to irradiation, the animals were placed in a light/dark-regulated habitat and had unrestricted access to soft food.

figure (3): anesthesia and irradiation of rats

Evaluation technique

Oral mucositis has been evaluated in both control and experimental groups. Pro-inflammatory indicators, involving interleukin-1β and TNF-α, together with SOD, were biochemically assessed in the serum of rats. Morphological alterations in mucosal tissues were evaluated at the microscopic level, and immunohistochemistry investigation of p53 expression was conducted on tissue samples from rats.

Clinical evaluation: All rats underwent examination immediately post-radiotherapy, as well as on the 7th and 14th days of the trial, with scores assigned based on the oral mucositis grading method established by Parkins et al.[14]

(Table 1). This research comprised three blinded assessors and one reviewer to mitigate bias.

I) Table 1 : Oral mucositis scoring system.

Score	Description
0	Normal
0.5	Slightly pink
1	Slightly red
2	Severe reddening
3	Focal desquamation
4	Exudate covering below one half of the irradiated mucosa
5	Virtually complete ulceration (**denuded**) of mucosa

II) Biochemical examination:

Pro-inflammatory markers [(TNF-α), (SOD), and(interleukin-1β)] were assessed in serum using the Enzyme-Linked ImmunoSorbent Assay (ELISA) technique at a wavelength of 450 nm. The serum samples have been allowed to coagulate at ambient temperature overnight at 4℃ prior to centrifugation for 15 minutes at 1000×g at 2~8℃. The supernatant was obtained for the test. The samples were incubated for ninety minutes at thirty-seven degrees Celsius, following which the liquid was discarded, and 100 microliters of biotinylated detection antibodies has been added and incubated for one hour at thirty-seven degrees Celsius. The samples have been washed and aspirated three times, after which 100 microliters of Horseradish Peroxidase (HRP) conjugate has been added and incubated for thirty minutes at thirty-seven degrees Celsius. The samples have been aspirated and rinsed five times. Additionally, ninety microliters of substrate reagent have been introduced and incubated for fifteen minutes at thirty-seven degrees Celsius. Subsequently, fifty microliters of stop solution have been added, and readings were promptly recorded at 450 nm to determine the results**.**

SOD levels were quantified in each sample using ELISA kits that use the WST-8 technique.[15] The WST-8 technique relies on the colorimetric response of WST-8. Xanthine oxidase (XO) catalyses the oxidation of xanthine, resulting in the formation of superoxide anion, which subsequently reduces WST-8 to generate water-soluble Formosan (a purple pigment). As SOD neutralizes superoxide anion, its activity impedes the total colorimetric response. Consequently, the inhibition levels serve as indicators of SOD activity in cells, tissues, or other biological specimens**.**

Statistical analysis:

Numerical information has been evaluated for normality through examining the information distribution and utilizing normality tests (Shapiro-Wilk tests and Kolmogorov-Smirnov). All information had a normal (parametric) distribution, however oral mucositis scores represented non-parametric data. Information has been reported as mean, median, standard deviation (SD), and range. A one-way Analysis of Variance (ANOVA) test has been used to compare the groups for parametric information. Bonferroni's post-hoc test has been used for paired comparisons after a significant ANOVA test. The Kruskal-Wallis test has been used to compare the groups for non-parametric information. The Friedman test has been applied to analyze the temporal variations in oral mucositis scores. Dunn's test has been applied for pairwise comparisons after significant results from the Kruskal-Wallis test or Friedman test. The significance threshold has been established at P below 0.05. Statistical analysis has been done utilizing IBM SPSS Statistics for Windows, Version 23.0. Armonk, New York: IBM Corporation

Results:

I. Clinical evaluation; oral mucositis index (OMI):

The influence of administration of CoQ10 on mucositis immediately after radiotherapy and on day 7 and day 14 after exposure was scored utilizing OMI developed by Parkins et al., and the information attained have been assessed (**Table 3**) (**Fig 4**)

Figure 4. Oral mucosal damage scoring in rats following radiation exposure, represented visually from grade 0 to 5. The grading scale is as follows: 0 – Slightly pink mucosa; 0.5 – Slightly red mucosa; 1 – Severe reddening of mucosa; 2 – Focal desquamation (peeling of surface layers); 3 – Exudate covering less than one half of the irradiated mucosa; 4 – Virtually complete ulceration (denudation) of the mucosa; 5 – Extensive tissue damage and severe ulceration.

The comparison of the measured values in three groups at increasing time points with reference to the time of radiation is presented in the **table 3**. Three groups had the same baseline (0) usually before radiation, as the median and mean, with p-value = 1 effect size (Eta squared) = 0, revealing no baseline variation. At 1 week after radiation there were statistically significant variances among the groups (p-value under 0.001, $\eta 2 = 0.152$), with Group II having the greatest median (3) and mean (2.8 ± 0.9) and Group III next [median 2, mean 1.8 ± 1.4), whereas Group I was at zero. In addition, 2 weeks after the radiation, these differences became more evident ($p < 0.001$, $Eta^2 = 0.174$), with Group II: median = 5 and mean = 4.5 ± 0.7 and with Group III: median = 4 and mean = 3 ± 2.2 and by contrast Group I did not change. The comparisons between groups in subsequent waves yielded a significant increase for Groups II (p below 0.001, w = 0.526) and III (p below 0.001, w = 0.096), whereas it remained stable for Group I (p = 1, w = 0). These results show that Groups II and III were subjected to major radiation-induced variations over time, while Group I was left unchanged.

II. Hematological evaluation

TNF-α and IL-1β

The comparison of IL-1β and TNF-α (pg./ml) concentrations in the three study groups has been presented in table 4 (one-way ANOVA test). The mean TNF-α levels were higher in group II (107.5 ± 2.6 pg/ml), followed by group III (92.7 ± 1.3 pg/ml) and Group I (64.2 ± 2.9 pg/ml). Similarly, group II showed the highest (63.4 ± 2.6 pg/ml) and group III the next highest (42.8 ± 1.3 pg/ml) levels of IL-1β, whereas group I demonstrated the least (25.7 ± 0.7 pg/ml). There were significant variances for both cytokines between the three groups ($p < 0.001$ for all). Further, the effect sizes were extremely high, with eta squared values that correspond to 0.984 for TNF-α and 0.989 for IL-1β, which demonstrate that 98.4% and 98.9%, respectively, of the variances in cytokine levels are accounted for by differences between groups. These results indicated a high correlation between group category and systemic inflammatory cytokine expressions.

III. Biochemistry evaluation

SOD (µ/ml)

The comparison of three groups on SOD levels (Group I, II and III; n = 13 each) was found to be highly significant (p below 0.001) which is strong evidence against the null hypothesis. In **Table 5**, Group I had the mean value of 1.85 ± 0.08, Group II had the lowest mean of 0.96 ± 0.03 while Group III had the highest mean (2.87 ± 0.08). The very low standard deviations among all groups indicate a close measurement among each group. High eta squared (=0.993) implies that the effect is very large, that 99.3% of variance can be assigned to group differences.

Table 3: Comparison between oral mucositis scores in the three groups and Friedman's test for the alterations within each group

Time	Group I (num. = 13)		Group II (num. = 13)		Group III (num. = 13)		*P*-value	*Effect size (Eta squared)*
	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)		
Before radiation	0 (0. 0) [F]	0 (0)	0 (0. 0) [F]	0 (0)	0 (0. 0)	0 (0)	1	0
1 week	0 (0. 0) [B]	0 (0)	3 (2, 5) [AE]	2.8 (0.9)	2 (0. 5) [AE]	1.8 (1.4)	<0.001*	0.152
2 weeks	0 (0. 0) [B]	0 (0)	5 (3, 5) [AD]	4.5 (0.7)	4 (0. 5) [AD]	3 (2.2)	<0.001*	0.174
***P*-value**	1		<0.001*		0.368			
Effect size (w)	0		0.526		0.096			

**: Significant at P below 0.05.*

Table 4: Comparative analysis between TNF-α and IL-1β concentrations (Pg/ml) in the three groups

Group I (num. = thirteen)		Group II (num. = thirteen)		Group III (num. = thirty)		*P*-value	*Effect size (Eta squared)*
TNF-α concentrations (Pg/ml)							
Mean	SD	Mean	SD	Mean	SD	<0.001*	0.984
64.2 [C]	2.9	107.5 [A]	2.6	92.7 [B]	1.3		
IL-1β concentrations (Pg/ml)							
Mean	SD	Mean	SD	Mean	SD	<0.001*	0.989
25.7 [C]	0.7	63.4 [A]	2.6	42.8 [B]	1.3		

Different superscripts indicate statistically significant variance between groups

Table 5: Comparison between SOD levels (µ/ml) in the three groups

Group I (num.= thirteen)		Group II (num.= thirteen)		Group III (num.= thirteen)		*P*-value	*Effect size (Eta squared)*
Mean	SD	Mean	SD	Mean	SD	<0.001*	0.993
1.85	0.08	0.96	0.03	2.87	0.08		

DISCUSSION

This work used robust statistical methods, including one-way ANOVA, Friedman's test, and Bonferroni post hoc comparison, to examine the effects of radiation and CoQ10 on oral mucositis, inflammatory cytokines, oxidative stress indicators, and histological changes. Marked disparities in all principal comparisons were seen across the three groups, with $p < 0.001$ at each endpoint.

CoQ10 has shown anti-inflammatory properties in many trials. It was shown to diminish the synthesis of inflammatory cytokines and TNF-α in both animal and human research. CoQ10 has been shown to ROS and enhance endothelial function, perhaps contributing to inflammatory development. 12, 14, 16 17, 18, 19 This study presents, for the first time, the impact of CoQ10 in preventing RIOM, since no previous research in the literature has assessed its efficacy in this context.

This research aimed to evaluate the impact of CoQ10 on preventing of RIOM in experimental rats. A dosage of 200 milligrams/kilogram of CoQ10 was chosen because to its neuroprotective properties. The absorption of CoQ10 is sluggish and constrained because of its hydrophobic nature and substantial molecular weight; hence, elevated doses are required to penetrate various rat organs.20 In the present investigation, we used several assessment techniques, including clinical, biochemical (IL-1β, TNF-α, and SOD), 14.17 SOD enzymes are crucial components of antioxidant defence, which has been a longstanding area of research in illness and the possible therapeutic enhancement of SOD levels.18

The current research's outcomes demonstrated a statistically significant decline in the mean concentration of TNF-α and IL-1β in group III compared to group II, suggesting that CoQ10 is an effective anti-inflammatory drug. This aligns with prior research by Mazidi M. et al., which posited that CoQ10 exerts its advantageous effects via both indirect and direct anti-inflammatory mechanisms; CoQ10 has been documented to modulate the gene expression of interleukin-1 and TNF-α. 18 Fan L, et al. demonstrated that the treatment of CoQ10 in dosages between 60 and 500 mg/day for an intervention period of one week to four months effectively reduced the production of inflammatory cytokines. The authors hypothesised that CoQ10 treatment reduced pro-inflammatory cytokines & inflammatory indicators in older individuals with reduced CoQ10 concentrations.21 Additional research corroborates the notion that CoQ10 has anti-apoptotic & anti-inflammatory properties via redox-dependent pathways, since supplementation with CoQ10 was

demonstrated to reduce plasma concentrations of interleukin-6, C-reactive protein (CRP), and TNF-α. Prior research indicated that the anti-inflammatory properties of CoQ10 may correlate with adiponectin; supplementation with CoQ10 results in elevated adiponectin levels, thus diminishing the inflammatory response mediated by TNF-α.22 And assist in safeguarding against the advancement of oxidative damage and mitochondrial impairment.23

Superoxide dismutase (SOD) is a crucial antioxidant enzyme. It eliminates free radicals and mitigates their toxicity. In Group III, SOD had a statistically significant elevated mean. Prior study by Carretero et al. (2017) and Komaki H. et al. (2019) established that several biological activities in organisms generate ROS, leading to oxidative stress. In reaction to oxidative stress, organisms may use SOD to eliminate ROS and so safeguard cellular equilibrium.24, 25 We determined that the elevated SOD levels in group III signify a reduced ROS concentration, indicating that coenzyme Q10 serves as an efficient antioxidant and anti-inflammatory prophylactic against the oxidative effects of head and neck radiation. 22, 24.

The antioxidant characteristics of CoQ10 may safeguard all cells and tissues, particularly those engaged in the adaptive & innate immunological responses. Oxygen species (OS) significantly contribute to immunological cytotoxicity against infections via the generation of ROS by macrophages. 26

Numerous constraints must be acknowledged. Initially, the radiation administered in our trial was a singular, elevated dosage of 15 Gy. The findings may be only relevant to the animal models. The length of medication administration and the follow-up period were quite brief. Additional long-term research are required to validate the effectiveness of CoQ10 supplementation as a powerful anti-inflammatory and antioxidant enzyme that inhibits RIOM.

CONCLUSION:

CoQ10 functions as a powerful antioxidant and anti-inflammatory mucoprotective agent, mitigating radiation-induced oral mucositis. Nonetheless, an increased number of clinical trials must be conducted to get conclusive determinations.

Recommendations:

We advise that subsequent studies employ lower fractionated doses instead of the single high radiation dose of 15 Gy, which replicates the effects of stereotactic body radiation therapy (SBRT) in treating head and neck squamous cell carcinoma (HNSCC), utilized in our study to investigate its preventive effects with fractionated low radiation doses. A prolonged follow-up would elucidate the durability of the impact, taking into account mucositis advancing to tissue healing.

Declarations:

Ethical Approval: local Ethics Committee of the Faculty of Dentistry, Minia University (Approval no 96-742-2023) and according to the internationally accepted principles of the public health service (PHS) policy on human care and use of laboratory animals.

Consent for Publication: not applicable.

Funding: no external funding has been received for this research

Conflict of Interest: no conflicts of interest.

Clinical Trial Number: not applicable

Availability of Data and Materials: The datasets generated and/or examined through the current research are available from the corresponding author on reasonable request

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