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Evaluating the Antioxidant Potential of Naringin in Combating Sodium Nitrite-Induced Heart dysfunction in male rats.

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Abstract
Sodium nitrite is extensively utilized as a food preservative; nevertheless, excessive exposure has been associated with oxidative stress. Citrus fruits naturally contain naringen, a flavonoid with strong anti-inflammatory and antioxidant qualities. In a rat model, this study sought to assess naringen ability to prevent sodium nitrite-induced heart oxidative dysfunction. Forty adult male rats were randomly divided into four groups: Rats in the control group (C) were given only food and water for the course of the investigation. Sodium Nitrite Group (G1): Rats were given oral sodium nitrite at a dose of 5 mg/kg/BW and, after three weeks, were given oral naringin at a dose of 25 mg/kg/BW. Rats in the naringin + sodium nitrite Group (G2) were given an oral dose of 25 mg/kg/Bw of naringin along with 5 mg/kg/Bw of sodium nitrite. Naringin Group (G3): During the trial, rats were given naringin orally at a dose of 25 mg/kg/BW. The results showed that oral intubation of Sodium nitrite for 45days induce oxidative heart stress, by a substantial elevated (P≤0.05) in troponin I, ck-mb , LDH , malondialdehyde MDA and decrease in GSH, whereas naringen was given orally showed a considerable decrease (P≤0.05) in cardiac markers and MDA with inceased in GSH. Histological examination revealed myocardial changes . Co-treatment with naringenin markedly attenuated these changes, restoring antioxidant levels and preserving cardiac damage tissue . The outcome of this study indicate that by improving the antioxidant defense system and maintaining myocardial structure, naringen significantly minimizes the harmful impact of sodium nitrite on heart tissue.

Keyword*: sodium nitrite, naringen, troponin I, lactate dehydrogenase ,Glutathione, melanodehyde*

INTRODUCTION

Sodium nitrite ($NaNO_2$) is an inorganic chemical extensively utilized in many industrial, medical, and culinary applications. It is most recognized for its function as a food preservative, limiting the proliferation of pathogenic bacteria, including Clostridium botulinum, while preserving the color and flavor of cured meats and successfully managing rancidity by obstructing lipid oxidation **(Sindelar & Milkowski, 2012)**. Processed meats, including bacon and sausages, are substantial sources of dietary nitrosamines owing to the use of sodium nitrite as a preservative **(Al-Okaily *et a*l., 2012)**. The consumption of sodium nitrite, especially from processed meats, constitutes a significant source of nitrosamine exposure. Research has associated this exposure with a heightened risk of gastrointestinal malignancies **(Song, Wu, & Guan, 2020)** In the stomach's acidic milieu, sodium nitrite can interact with food amines or amines generated by gut microbes to synthesize nitrosamines. This internal development is affected by dietary intake and the nature of the gut microbiome **(Zhao & Wang, 2020)**. Sodium nitrite acts as a precursor to nitric oxide (NO), an essential signaling molecule in the body Signs ranging from cyanosis to coma might be observed in cases of severe methemoglobinemia linked to continuous consumption of sodium nitrite. **(Abed-Alazeez, *et al.*, 2016)** Oxidative stress (OS) corresponds to a disorder characterised by intensified cell injury associated with reactive oxygen species (ROS). **(Alwan & Al-Okialy, 2018)**. Reactive oxygen species (ROS) govern cell proliferation, inflammation, immunological response, and other critical physiological functions; yet, excessive ROS production results in oxidative stress **(Liu *et al.* 2023)**. Naringin is a naturally occurring flavonoid glycoside derived from grapefruit and oranges. It is part of a class of flavonoids characterized by a C6-C3-C6 fifteen-carbon structure, which are well-documented for their anti-inflammatory properties and ability to inhibit the activity of reactive oxidants **(Zhao and Liu, 2021)**.

MATERIAL AND METHODS

Animals and housing:

In this study, 40 adult Wister albino rats weighing 250+_20 g and aged 16–18 weeks were used. they were acclimatized in animal house of the college of veterinary medicine/university of Baghdad and rats for the experiment They were accommodated in a room with good ventilation within plastic cages, supplied with daily pellet feed with access to drinking water ad libitum throughout the duration of the study. The room temperature was preserved at 25°C for 12 hours during the light/dark cycle during the entire experimental period. Ethics committee of the faculty of veterinary Medicine of Baghdad /Baghdad university (reference number P.G/2265 in 27/11/2024).

Experimental design:

The duration of experiment 45 days 40 male rats selected randomly and divided into Four equal groups:
1-Control Group(C): Rats receiving only the food and water for the duration of the study.
2-Sodium Nitrite Group(G1): Rats receiving sodium nitrite 5mg/kg/BW orally and after 3 weeks treated orally by naringin 25 mg/kg/BW **(Kumara and Ajay,2019)** for 3 weeks .
3-Naringin + Sodium Nitrite Group(G2): Rats receiving a dose of naringin 25mg/kg/Bw orally **(Kumara and Ajay,2019)** in combination with sodium nitrite 5mg/kg/Bw .
4-Naringin Group (G3): Rats receiving only naringin 25mg/kg/BW orally (Kumara and Ajay,2019) for period of the experiment .

Biochemical analysis.

1-Troponin I was detailed in a lab ELIZA kit that was obtained from company Cloude-Clone Corp. China
2- Creatine Kinase (ck-mb) and Lactate dehydrogenase(LDH) was examined by used Rat Eliza kit from (Elabscience) /China
3- Melanodehyde (MDA) and Glutathione GSH described using a lab ELIZA kit that was from Elabscience / China

Tissue preparation for histopathological examination

To conduct histological examinations, as soon as the animals were euthanized, the heart and aorta were removed, blotted, opened and the specimen were fixed in 10% formaline for routine histopathological examination. 5-6 sections were stained with Hematoxyline-Eosin stain (H&E)

Statistical analysis

The Statistical Analysis System- SAS (2018) program was used to detect the effect of difference factors in study parameters. Least significant difference-LSD was used to significant compare between means (ANOVA/ two way) in this study **(SAS Institute, 2018).**

RESULT

1-Cardiac markers

A-Troponin I

The results in table (1) explained the serum Troponin I in control and treated groups. There are significant p≤o.o5 increased in 3 weeks after treated with SN group compared with zero and 6 weeks, also which showed elevation p≤0.05 significantly in (G1) compared with control , G2(sodium nitrite +naringen) and G3 (naringen) groups .

Table 1. Effect of sodium nitrite and naringin in serum Troponin I (pg/ml) in Adult Rats

Groups	Zero time	3 weeks	6 weeks
C	226.74 ±0.85 A a	227.51 ±0.85 B a	227.22 ±0.68 A a
G1	226.39 ±0.97 A b	429.27 ±0.59 A a	120.51 ±10.37 B c
G2	226.28 ±1.04	298.35 ±13.20	231.73 ±21.36

	A b	B a	A b
G3	225.19 ±0.28 A b	252.04 ±1.92 B a	110.89 ±3.71 B b

L.S.D.= 24.922 *

Values expressed as SE n=10
Control Grou p : 10 Rats receiving only the food and water for the duration of the study.,G1=10 Rats gavage sodium nitrite 5mg/kg/BW for 3 weeks ,then treated for 3 weeks with naringin 25 mg/kg/BW orally.,G2=10 Rats receiving naringin 25mg/kg/Bw orally concurrently with sodium nitrite 5mg/kg/Bw ,G3=10 Rats receiving naringin 25mg/kg/BW orally for six weeks of the experiment.,Capital litters denote significantly differences between groups (p≤0.05),small litters denote significantly differences within groups(p≤0.05)

B- Creatine Kinase-MB (CK-MB)

Rats exposed to sodium nitrite showed a significant increase in serum levels of creatine kinase-MB (CK-MB) compared to the control group (p≤0.05),G2 and G3groups . However, animals pretreated with naringen exhibited a marked reduction in these markers, specially in 6 weeks indicating a protective effect on cardiac tissue compared with 3 weeks and zero time .

Table 2. Effect of sodium nitrite and naringin in serum ck-mb (pg/ml) in Adult Rats

Groups	Zero time	3 weeks	6 weeks
C	122.70 ±8.87 A a	122.87 ±8.94 C a	122.37 ±8.81 AB a
G1	128.19 ±5.65 A b	849.84 ±17.49 A a	109.09 ±3.27 B b
G2	128.20 ±5.61 A b	155.34 ±6.10 B a	142.62 ±4.13 A ab
G3	128.04 ±5.63 A a	131.69 ±7.89 C a	141.82 ±4.50 A a

L.S.D.= 22.885 *

Values expressed as SE n=10
Control Grou p : 10 Rats receiving only the food and water for the duration of the study.,G1=10 Rats gavage sodium nitrite 5mg/kg/BW for 3 weeks ,then treated for 3 weeks with naringin 25 mg/kg/BW orally.,G2=10 Rats receiving naringin 25mg/kg/Bw orally concurrently with sodium nitrite 5mg/kg/Bw ,G3=10 Rats receiving naringin 25mg/kg/BW orally for six weeks of the experiment.,Capital litters denote significantly differences between groups (p≤0.05),small litters denote significantly differences within groups(p≤0.05)

C-Lactate dehydrogenase (LDH)

Exposed of ($NaNO_2$) resulted in table (3) a significant elevation of serum lactate dehydrogenase (LDH) levels compared to the zero time and 6 weeks (p≤0.05), indicating cellular damage and cardiac tissue injury. However, rats that received naringenin either as a co-treatment(G2) or as a pre-treatment(G3) showed a marked reduction($p \leq 0.05$) in LDH activity when compared to the sodium nitrite-(G1) group.

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Table 3. LD Effect of sodium nitrite and naringin in serum LDH (ng/ml) in Adult Rats

Group	Zero time	3 weeks	6 weeks
C	3.15 ±0.16 A a	3.28 ±0.14 C a	3.17 ±0.09 B a
G1	2.40 ±0.13 B b	8.45 ±0.29 A a	2.72 ±0.17 B b
G2	3.42 ±0.11 A b	5.12 ±0.16 B a	3.63 ±0.16 A b
G3	3.15 ±0.16 A b	3.71 ±0.21 C a	2.72 ±0.24 B b

L.S.D.= 0.499 *

Values expressed as SE n=10
Control Grou p : 10 Rats receiving only the food and water for the duration of the study.,G1=10 Rats gavage sodium nitrite 5mg/kg/BW for 3 weeks ,then treated for 3 weeks with naringin 25 mg/kg/BW orally.,G2=10 Rats receiving naringin 25mg/kg/Bw orally concurrently with sodium nitrite 5mg/kg/Bw ,G3=10 Rats receiving naringin 25mg/kg/BW orally for six weeks of the experiment.,Capital litters denote significantly differences between groups (p≤0.05),small litters denote significantly differences within groups(p≤0.05)

2-Oxidative status

A- Malondialdehyde (MDA)

Table (4) showed indicates an increase(p≤0.05) in oxidative stress and membrane lipid damage induced by sodium nitrite exposure .sodium nitrite treated group (G1) compared to the control group ,G2 and G3) This Conversely, administration of (NAR) with sodium nitrite resulted in a significant reduction in MDA levels ($p \leq 0.05$) compared to the $NaNO_2$ group. The MDA concentrations in the NAR+ $NaNO_2$ group were nearly comparable to the control group, suggesting that naringenin effectively mitigated lipid peroxidation.

Table 4. Effect of sodium nitrite and naringin in serum MDA (ng/ml) in Adult Rats.

Groups	Mean ±SE of MDA		
	Zero time	3 weeks	6 weeks
C	81.83 ±0.17 A a	81.33 ±0.37 C a	81.70 ±0.23 B a
G1	81.83 ±0.31 A c	485.58 ±35.39 A a	125.54 ±21.73 A b
G2	81.25 ±0.31 A b	143.32 ±3.17 B a	128.27 ±.88 A a
G3	81.29 ±0.28 A a	82.45 ±1.34 C a	83.06 ±1.54 B a

L.S.D.= 34.405 *

Values expressed as SE n=10
Control Grou p : 10 Rats receiving only the food and water for the duration of the study.,G1=10 Rats gavage sodium nitrite 5mg/kg/BW for 3 weeks ,then treated for 3 weeks with naringin 25 mg/kg/BW orally.,G2=10 Rats receiving naringin 25mg/kg/Bw orally concurrently with sodium nitrite 5mg/kg/Bw ,G3=10 Rats receiving naringin 25mg/kg/BW orally for six weeks of the experiment.,Capital litters denote significantly differences between groups (p≤0.05),small litters denote significantly differences within groups(p≤0.05)

B-Glutathione (GSH)

A significant decrease in reduced glutathione (GSH) levels was observed in table(5)the G1 group indicating severe depletion of the antioxidant defense system due to increased oxidative stress compared to the control ($p \leq 0.05$), G2 and G3 groups . However, rats treated with naringen along with sodium nitrite(G2) showed a marked restoration of GSH levels ($p \leq 0.05$). The GSH concentrations in the NAR+$NaNO_2$ group were significantly higher than those in the $NaNO_2$ appear in 6 weeks compared with 3 weeks and zero time .

Table 5: Effect of sodium nitrite and naringin in serum glutatione (ng/ml) in Adult Rats.

Group s	Zero time	3 weeks	6 weeks
C	17.56 ±0.36 A a	17.83 ±0.25 A a	17.76 ±0.29 B a
G1	16.87 ±0.56 A b	4.35 ±0.59 C c	20.72 ±1.91 A a
G2	16.90 ±0.41 A a	15.58 ±0.39 B a	17.14 ±0.33 B a
G3	17.87 ±0.47 A b	16.07 ±0.81 AB b	22.29 ±0.50 A a
L.S.D.= 2.026 *			

Values expressed as SE n=10

Control Grou p : 10 Rats receiving only the food and water for the duration of the study.,G1=10 Rats gavage sodium nitrite 5mg/kg/BW for 3 weeks ,then treated for 3 weeks with naringin 25 mg/kg/BW orally.,G2=10 Rats receiving naringin 25mg/kg/Bw orally concurrently with sodium nitrite 5mg/kg/Bw ,G3=10 Rats receiving naringin 25mg/kg/BW orally for six weeks of the experiment.,Capital litters denote significantly differences between groups ($p \leq 0.05$),small litters denote significantly differences within groups($p \leq 0.05$)

Histopathological changes

Histological examination of cardiac tissues in (figures) showed the sodium nitrite group (G1)revealed degenerative changes, these pathological alterations were notably attenuated in the G2 and group(G3), which showed nearly normal myocardial architecture and reduced cellular damage compared with control group.

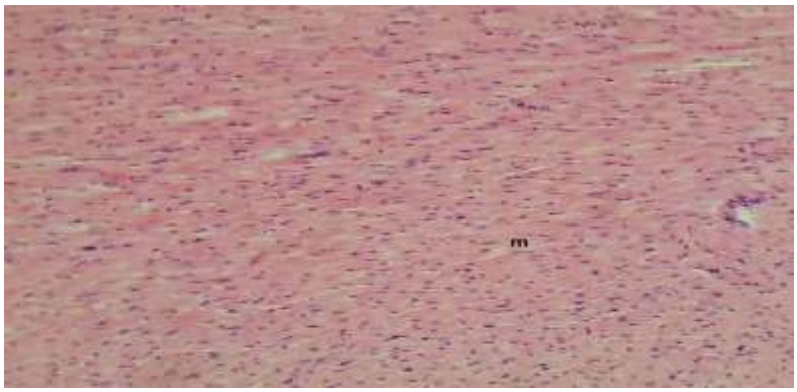
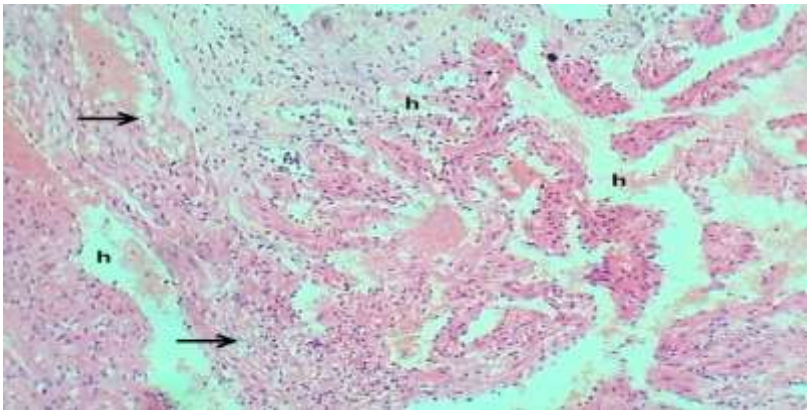
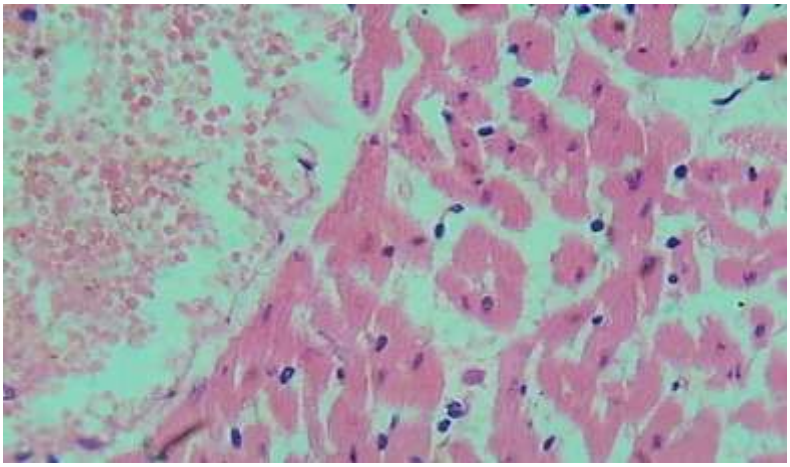


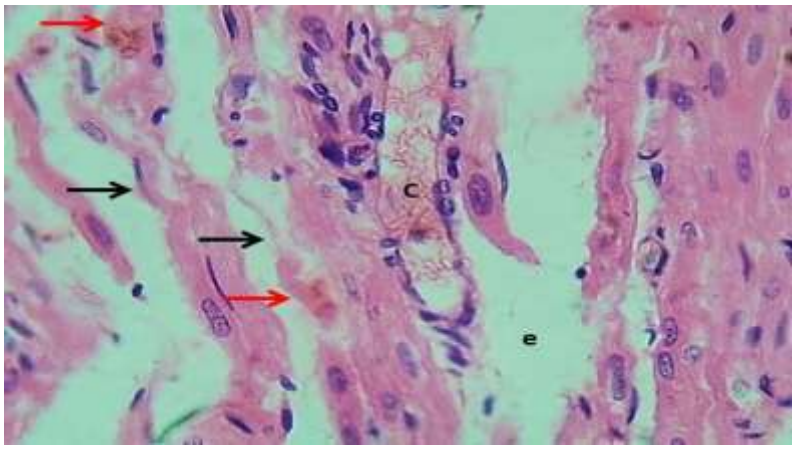
Figure 1: section of heart (Control) shows normal appearance & arrangement of myofibers (m).H&E.100



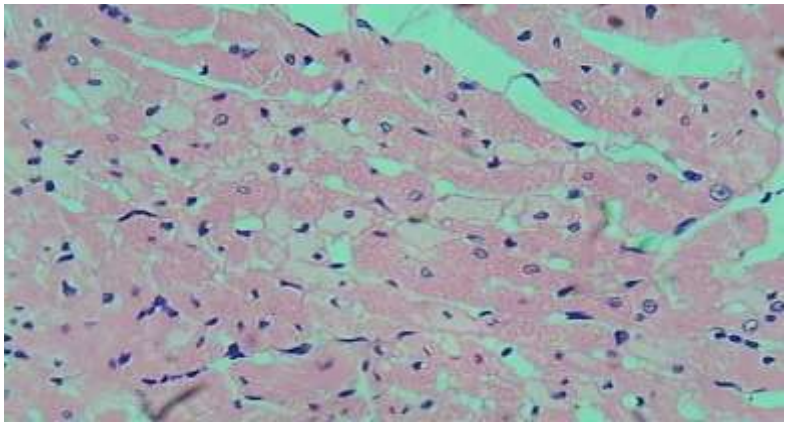
Fiqure 2:section of heart (group-Sodium nitrite) shows severe myocardial degeneration with necrosis with fibroplasia (Arrows) & hemorrhage (h). H&E stain.40x



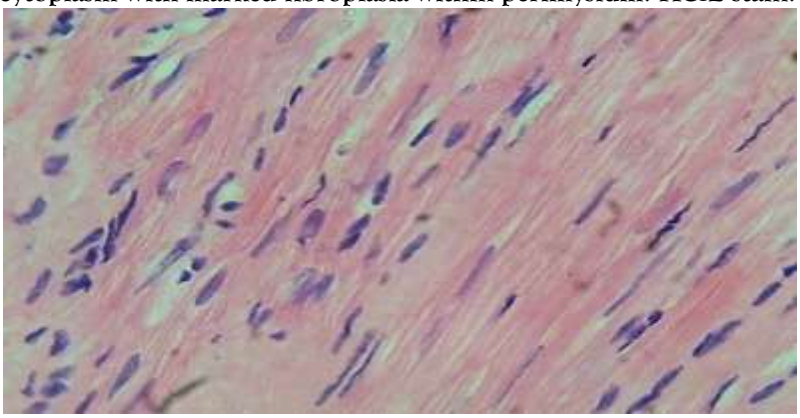
Fiqure 3:section of heart (Group-Sodium nitrite) shows severe myocardial degeneration with necrosis & hemorrhage. H&E stain.400x



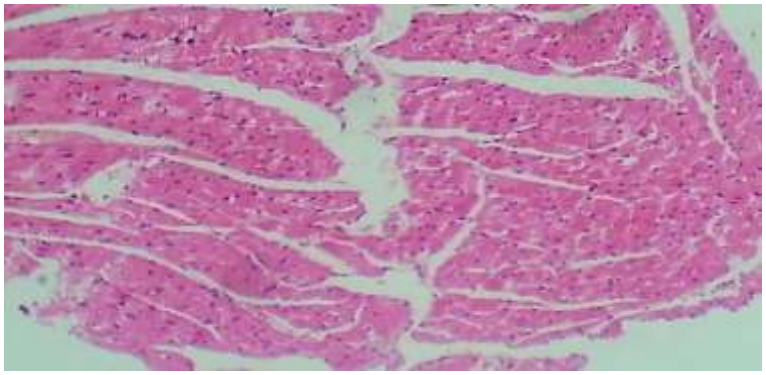
Fiqure 4:section of heart (sodium nitrite) shows moderate degeneration with necrosis of myofibers (Black arrows) & increased area of connective tissue with little histocytes & lymphocytes (e), congested blood vessels (C,) & tear (red arrows). H&E stain.400x



Fiqure 5:section of heart (group treatment with naringin) shows normal arrangement of myofibers that revealed vaculated cytoplasm with marked fibroplasia within perimysium. H&E stain.400x



Fiqure 6:section of heart (naringin) shows normal appearance with arrangement of myocardium myofibers & fibroblasts. H&E stain.400x



Fiqure 7:section of heart (sodium nitrite +naringin) shows normal arrangement of myofibers with little posts of degeneration. H&E stain.100x

DISCUSSION

The troponin complex has a location on the thin filaments of striated muscle cells alongside actin and tropomyosin. heart cellular troponin (cTn) acts as a precise and sensitive indicator to evaluate heart damage **(Berridge *et al.* 2009)**. The serum troponin-I concentrations in sodium nitrite-treated rats were markedly elevated in comparison to those found in normal rats. Nitrite could stimulate stress caused by oxidation in cells based on boosting the accumulation of molecules called reactive oxygen species (ROS). The abnormal genesis of stress-triggered reactive oxygen species (ROS) can indirectly harm critical biomacromolecules in the host, including DNA(through oxidation), and lipids (by a factor peroxidation), thereby triggering several types

of processes that ultimately result in disrupted cellular performance **(Gao et al., 2020)**. for instance superoxide radical (O2-) and hydrogen peroxide (H2O2). Reactive oxygen species (ROS) act alongside multiple signalling processes, which may impair ventricular microvascular circulation, leading to cardiac ischaemia, cardiac troponin I release, and ventricular disorders(**Mehri *et al.* 2023)**. Naringin notably decreased the serum troponin-I amounts, signifying cardioprotection endorsed by academicians **(Papasani *et al.*, 2014)**. our study, the high increase in cardiac enzyme(CK-MB) activity due to the effect of sodium and its causing damage to the heart, which leads to an increase in cardiac enzymes, indicating the occurrence of damage and cellular toxicity in the heart(**Fadda *et al.,* 2017)** The excessive creation of reactive oxygen species (ROS) induces oxidative damage to biological components, including DNA, lipids, proteins, and basement membranes, resulting in cellular and organ malfunction. **(Khudiar, Abdullah, & Al-Mzaien, 2001)**.A number of protease enzymes might become activated and calcium influx might get enhanced in the presence of oxidative and nitrosative stress. This may directly or indirectly lead to changes in cellular proteins and gene expression, thus reducing heart function. .The free radical production system, both oxyradicals and hydrogen peroxide, has been found to inhibit sarcolemmal Na+ -K+ ATPase, Na+ -Ca2+ exchange through rising lipid peroxidation and sulfhydryl group modification. **(Kaneko *et al.*, 1989)**. While reduced in activity of both of Ca2+-uptake and Ca2+-pump ATPase via oxyradicals and hydrogen peroxide. This system explains the mechanism of cellular damage in the heart through failure of oxidative phosphorylation in mitochondria as well as reduction in myofibrillar and Oxidative stress induced by hydrogen peroxide (H2O2) leads to cellular death and initiates apoptosis owing to DNA damage. **(Khalil, Alol, & Obead, 2013)** .In rats treated with naringin, observed an improvement in the levels of both CK and LDH **(Khodayar *et al.,* 2018)**, which indicates that the cardiac cell resists necrosis **(Muthumani & Prabu, 2014)**. naringin has the property of resisting oxidative stress by reducing the activity of the enzyme myeloperoxidase and also regulates and improves the levels of SOD and MDA.

The effect of sodium nitrite on treated rats (G1) showed a significant decrease in glutathione(GSH) levels and an increase in MDA activity. Nitrite exerts oxidative stress, which leads to the generation of free radicals **(Al-Gayyar *et al.*, 2014)**). The decreased serum glutathione levels in the treated rats (G1) group with NANO2 were due to the creation of oxidized lipids **(Shahjahan *et al.*, 2005)** MDA is considered a key marker in accurately detecting cellular damage and oxidative stress **(Carampin *et al.,* 2003)** Lipid peroxidation (LPO) is caused by the breakdown of fats, mainly due to the radical bodies, which can occur enzymatically or nonenzymatically. This phenomenon is closely associated with oxidative stress, leading to cellular damage and the generation of harmful by products such as malondialdehyde (MDA) Lipid peroxide, referred to as MDA, is capable of destroying enzymes and DNA**(Al-Tamemi & Al-Okaily, 2025; Ascar *et al.,* 2022)**. Inflammatory reactions resulting from reactive oxygen species (ROS) creation are crucial phases in the development of atherosclerotic plaques **(Dheyab, Arrak, & Al-Qayim, 2025)**

Histopathological changes:

The histopathological analysis of cardiac tissues provided clear evidence of sodium nitrite-induced myocardial damage and the protective effects of naringenin. In the sodium nitrite-treated group (fiqure 2,3and 4) the heart sections showed marked structural alterations, including disorganization of myocardial fibers, interstitial edema, vascular congestion, and infiltration of inflammatory cells. These pathological changes are consistent with previous reports demonstrating that nitrite exposure leads to oxidative damage through the generation of reactive oxygen species (ROS), lipid peroxidation, and impairment of mitochondrial function in cardiac cells **(Atef and Youssef, 2015)**. In contrast, co-administration of naringin significantly ameliorated these histopathological changes. Cardiac tissues from rats treated with both sodium nitrite and naringen (**fiqure 7**) exhibited nearly normal architecture, with preserved myocardial fibers, reduced inflammatory infiltration, and minimal vascular congestion**(Khan *et al,.*2020)** These findings strongly support the antioxidant and anti-inflammatory properties of naringen, ,which may act by scavenging free radicals, enhancing endogenous antioxidant enzyme activity Furthermore, naringen may exert protective effects by modulating signaling pathways involved in oxidative stress and inflammation see in fiqure **(5 and 6).**

CONCLUSION

stress and tissue damage, as evidenced by elevated MDA and LDH levels and depleted GSH concentrations. These alterations reflect enhanced lipid peroxidation, cellular injury, and compromised antioxidant defense mechanisms. Importantly, co-treatment with naringen markedly attenuated these harmful effects. Naringen significantly reduced MDA and LDH ,ck-mb and troponin I levels while restoring GSH levels toward normal values, suggesting its strong antioxidant and cyto -protective properties

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Novelty statement

Novelty of Research focuses on the cardioprotective effect of naringin as a supplement against oxidative stress of sodium nitrite and the elucidation effects of a nutritional supplement of naringin that can be used as a treatment to reduce oxidative stress in disease.

Authors contribution: These authors each contributed equally

Conflict of interest: The authors have declared no conflict of interest.

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