

The Effect of Melatonin on Oxidative Biomarkers (MDA,SOD,GSH) in Patients with Stable Angina

Zahraa R. Hadi¹ and Layth Jabbar¹

Oxidative Stress
Biomarkers and
Clinical
Improvement in
Stable Angina

ABSTRACT

Objective: To investigate the relationship between change in oxidative stress markers and change in angina symptom burden and sleep quality in patients with stable angina given adjunctive melatonin therapy

Study Design: Randomized, quadruple blind, placebo-controlled Study

Place and Duration of Study: This study was conducted at the College of Pharmacy, University of Thi-Qar, Iraq from 1st February 2026 to 30th April 2026

Methods: One hundred patients were enrolled, among them 55 patients taking melatonin 5 mg once daily at night and 45 taking placebo, in addition to usual anti-anginal treatment. Oxidative stress markers were malondialdehyde, superoxide dismutase and glutathione. Clinical measures were the number of angina episodes per week, angina severity, short-acting nitrate use, and Pittsburgh Sleep Quality Index.

Results: In the melatonin group, malondialdehyde decreased from 4.82 ± 0.91 to 3.79 ± 0.81 $\mu\text{mol/L}$, while superoxide dismutase increased from 6.21 ± 1.15 to 7.15 ± 1.20 U/mL and glutathione from 38.7 ± 6.5 to 44.8 ± 7.1 $\mu\text{mol/L}$. Weekly angina episodes decreased from 3.4 ± 1.7 to 1.3 ± 1.1 , short acting nitrate use from 3.0 ± 1.8 to 1.0 ± 1.1 doses/week, and Pittsburgh Sleep Quality Index from 9.1 ± 3.0 to 6.2 ± 2.7 .

Conclusion: Favourable changes in oxidative stress biomarkers, particularly reduced malondialdehyde and increased glutathione, were associated with improved angina symptoms and sleep quality.

Key Words: Melatonin, Oxidative stress, Stable angina, Malondialdehyde, Superoxide dismutase, Glutathione, Angina symptoms, Pittsburgh Sleep Quality Index.

Citation of article: Hadi ZR, Jabbar L. The Effect of Melatonin on Oxidative Biomarkers (MDA,SOD,GSH) in Patients with Stable Angina. Med Forum 2026;37(9):26-30. doi:10.60110/medforum.370905.

INTRODUCTION

It has traditionally been explained by fixed atherosclerotic constriction of the epicardial coronary arteries but recent evidence has focused on a more complex pathophysiology, which involves stenosis, coronary microvascular dysfunction, vasomotor abnormalities, endothelial dysfunction, inflammation, and altered myocardial oxygen supply-demand balance^{1,2}. The view of oxidative stress as a biologically relevant pathway in coronary artery disease is gaining momentum since overproduction of reactive oxygen

species can limit the bioavailability of nitric oxide, enhance endothelial dysfunction, oxidize lipids and lipoproteins, increase vascular inflammation and promote atherosclerotic plaque development and destabilization^{3,4}. Malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH) are commonly employed to reflect different aspects of redox biology: lipid peroxidation, antioxidant enzymes and non-enzymatic antioxidant stores^{5,6}.

Melatonin may directly contribute to the reactive oxygen and nitrogen species scavenging, mitochondrial activity, endogenous antioxidant defenses, and inflammatory signaling pathways, which are pertinent to cardiovascular disease^{7,8}. Some altered melatonin physiology in patients with coronary artery disease and possible protective effect against ischemia have also been proposed by observational and clinical studies⁹.

Unstable angina, clinically it is important to know whether the change in the frequency of oxidative stress markers is similar to the change in the frequency of angina attack, use of nitrates, functional symptoms category, and quality of sleep¹⁰.

The hypothesis was that greater reduction in malondialdehyde and greater increases in superoxide dismutase and glutathione would be associated with larger reductions in weekly angina frequency, angina

¹. MSc Scholar / Assistant Professor², Department of Pharmacognosy, College of Pharmacy, University of Thi-Qar, Thi-Qar, Iraq

Correspondence: Layth Jabbar, Assistant Professor, Department of Pharmacognosy, College of Pharmacy, University of Thi-Qar, Thi-Qar, 64001, Iraq.
Contact No: 009647705512899
Email: layth.jabbar@utq.edu.iq

Received: May, 2026

Reviewed: June-July, 2026

Accepted: August, 2026

severity, short-acting nitrate use, and Pittsburgh Sleep Quality Index global score.

METHODS

This was a randomized, quadruple blind, placebo-controlled trial was conducted at College of Pharmacy, University of Thi-Qar, Iraq from 1st February 2026 to 30th April 2026 vide letter No. IQ.UTQ.PHARM.2025.005 dated 19th January 2026. One hundred patients were enrolled, among them 55 patients taking melatonin 5 mg once daily at night and 45 taking placebo, in addition to usual anti-anginal treatment. The administration at bedtime was selected based on the physiological functions of melatonin in circadian regulation and sleep-wake rhythm as well as allowing the assessment of its antioxidant and cardiometabolic significance. The biomarker panel included malondialdehyde, superoxide dismutase, and glutathione. MDA was measured in $\mu\text{mol/L}$ and was interpreted as a marker of lipid peroxidation. SOD was measured in U/mL and was interpreted as an enzymatic antioxidant defense marker. GSH was measured in $\mu\text{mol/L}$ and was interpreted as a non-enzymatic antioxidant marker. Fasting morning samples were preferred to reduce variability related to recent food intake and circadian effects. Samples were processed promptly and stored according to laboratory requirements for oxidative stress assays. Angina symptom burden was assessed using a standardized angina diary, while functional severity was summarized using Canadian Cardiovascular Society class. These approaches are consistent with commonly used symptom-based assessment in chronic stable angina. A participant with a large negative ΔMDA would be considered to have greater reduction in lipid peroxidation, while a participant with a large positive ΔGSH would be considered to have greater improvement in antioxidant reserve. This exploratory approach is biologically justified because oxidative stress, endothelial dysfunction, microvascular impairment, and sleep disturbance may interact in chronic coronary syndromes, but the analysis should be interpreted as hypothesis-generating rather than confirmatory.

RESULTS

There were 55 in melatonin arm and 45 in the placebo arm (Table 1). MDA decreased from $4.82 \pm 0.91 \mu\text{mol/L}$ at baseline to $3.79 \pm 0.81 \mu\text{mol/L}$ at week 8 in the melatonin group, giving a mean change of $-1.03 \pm 0.72 \mu\text{mol/L}$. In the placebo group, MDA decreased only slightly from $4.76 \pm 0.88 \mu\text{mol/L}$ to $4.55 \pm 0.90 \mu\text{mol/L}$, with a mean change of $-0.21 \pm 0.60 \mu\text{mol/L}$. The between-group difference in MDA change was statistically significant, indicating a greater reduction in lipid peroxidation among patients receiving melatonin. SOD activity increased from $6.21 \pm 1.15 \text{ U/mL}$ to

$7.15 \pm 1.20 \text{ U/mL}$ in the melatonin group, compared with a smaller increase from $6.18 \pm 1.09 \text{ U/mL}$ to $6.36 \pm 1.08 \text{ U/mL}$ in the placebo group. Similarly, GSH increased from $38.7 \pm 6.5 \mu\text{mol/L}$ to $44.8 \pm 7.1 \mu\text{mol/L}$ in the melatonin group, whereas the placebo group showed only a modest increase from $39.1 \pm 6.2 \mu\text{mol/L}$ to $40.2 \pm 6.6 \mu\text{mol/L}$ (Table 2).

Table No. 1: Baseline characteristics of the analyzed participants

Variable	Melatonin group (n = 55)	Placebo group (n = 45)
Age (years)	58.4 ± 7.3	57.9 ± 7.8
Male sex	33 (60%)	28 (62.2%)
BMI (kg/m^2)	29.4 ± 3.6	29.1 ± 3.9
Hypertension	38 (69.1%)	32 (71.1%)
Diabetes mellitus	23 (41.8%)	20 (44.4%)
Dyslipidemia	42 (76.4%)	35 (77.8%)
Current smoker	15 (27.3%)	11 (24.4%)
Beta-blocker use	44 (80%)	37 (82.2%)
Calcium channel blocker use	28 (50.9%)	22 (48.9%)
Long-acting nitrate use	31 (56.4%)	26 (57.8%)
Statin use	48 (87.3%)	40 (88.9%)
Weekly angina episodes	3.4 ± 1.7	3.3 ± 1.8
PSQI global score"	9.1 ± 3.0	9.3 ± 3.2

Table No. 2: Oxidative stress biomarkers at baseline, week 4, and week 8

Biomarker	Time point	Melatonin group (n=55)	Placebo group (n=45)	P value
MDA ($\mu\text{mol/L}$)	Baseline	4.82 ± 0.91	4.76 ± 0.88	0.74
	Week 4	4.21 ± 0.86	4.63 ± 0.87	0.018
	Week 8	3.79 ± 0.81	4.55 ± 0.90	<0.001
	Mean change	-1.03 ± 0.72	-0.21 ± 0.60	<0.001
SOD (U/mL)	Baseline	6.21 ± 1.15	6.18 ± 1.09	0.89
	Week 4	6.78 ± 1.18	6.29 ± 1.11	0.037
	Week 8	7.15 ± 1.20	6.36 ± 1.08	0.001
	Mean change	$+0.94 \pm 0.83$	$+0.18 \pm 0.69$	<0.001
GSH ($\mu\text{mol/L}$)	Baseline	38.7 ± 6.5	39.1 ± 6.2	0.76
	Week 4	41.9 ± 6.8	39.8 ± 6.4	0.12
	Week 8	44.8 ± 7.1	40.2 ± 6.6	0.001
	Mean change	$+6.1 \pm 5.4$	$+1.1 \pm 4.9$	<0.001

The clinical improvement indicated that improvement in oxidative biomarkers occurred alongside clinically meaningful improvement in angina symptom burden, rescue nitrate use, and subjective sleep quality (Table 3).

Correlation between biomarker changes and clinical changes: Increases in SOD and GSH were inversely associated with clinical change scores, because positive changes in antioxidant markers were associated with

negative changes in angina outcomes and PSQI (Table 4).

Regression analysis: In the model for change in weekly angina episodes, both Δ MDA and Δ GSH remained

independently associated with symptom improvement after adjustment for baseline angina frequency, age, sex, diabetes mellitus, hypertension, and treatment group (Table 5).

Table No. 3: Clinical outcome changes from baseline to week 8

Clinical outcome	Melatonin baseline	Melatonin week 8	Mean change	Placebo baseline	Placebo week 8	Mean change	Between-group p-value
Weekly angina episodes	3.4 $\pm$ 1.7	1.3 $\pm$ 1.1	-2.1 $\pm$ 1.4	3.3 $\pm$ 1.8	2.7 $\pm$ 1.6	-0.6 $\pm$ 1.2	<0.001
Angina severity score	6.1 $\pm$ 1.4	3.8 $\pm$ 1.6	-2.3 $\pm$ 1.5	6.0 $\pm$ 1.5	5.2 $\pm$ 1.7	-0.8 $\pm$ 1.3	<0.001
Nitrate use/week	3.0 $\pm$ 1.8	1.0 $\pm$ 1.1	-2.0 $\pm$ 1.3	2.9 $\pm$ 1.7	2.4 $\pm$ 1.5	-0.5 $\pm$ 1.1	<0.001
PSQI global score	9.1 $\pm$ 3.0	6.2 $\pm$ 2.7	-2.9 $\pm$ 2.4	9.3 $\pm$ 3.2	8.7 $\pm$ 3.0	-0.6 $\pm$ 2.1	<0.001

Table No. 4: Correlations between oxidative biomarker changes and clinical outcome changes

Biomarker change	Δ Weekly angina episodes	Δ Angina severity	Δ Nitrate use/week	Δ PSQI score
Δ MDA	r = 0.46, p<0.001	r = 0.39, p<0.001	r = 0.42, p<0.001	r = 0.44, p<0.001
Δ SOD	r = -0.28, p=0.005	r = -0.24, p=0.016	r = -0.26, p=0.009	r = -0.22, p=0.028
Δ GSH	r = -0.43, p<0.001	r = -0.36, p<0.001	r = -0.38, p<0.001	r = -0.41, p<0.001

Table No. 5: Multivariable regression models for predictors of clinical improvement

Dependent variable	Predictor	B coefficient	95% CI	Standardized β	p-value
Δ Weekly angina episodes	Δ MDA	0.42	0.15 to 0.69	0.31	0.003
	Δ GSH	-0.06	-0.11 to -0.02	-0.27	0.010
	Baseline angina frequency	-0.18	-0.32 to -0.04	-0.25	0.013
	Diabetes mellitus	0.21	-0.19 to 0.61	0.10	0.30
	Melatonin group	-0.78	-1.33 to -0.23	-0.29	0.006
Δ PSQI score	Δ MDA	0.72	0.27 to 1.17	0.34	0.002
	Δ GSH	-0.10	-0.18 to -0.02	-0.26	0.015
	Baseline PSQI	-0.23	-0.36 to -0.10	-0.33	0.001
	Diabetes mellitus	0.34	-0.38 to 1.06	0.09	0.35
	Melatonin group	-1.12	-2.02 to -0.22	-0.27	0.015

DISCUSSION

The contribution of oxidative stress to endothelial dysfunction, atherosclerosis, microvascular dysfunction and coronary symptom burden^{11,12}. Reduced MDA could be an indication of decreased lipid peroxidation and decreased oxidative damage of vascular and cell membranes, whereas increased GSH and SOD activity could reflect enhanced antioxidant protection and the redox balance^{5,6}. Since nitric oxide signaling and endothelial activity are vulnerable to oxidative stress, redox status can be improved, which can positively influence vascular tone and myocardial perfusion reserve^{13,14}.

Patients whose lipid peroxidation is reduced larger or whose antioxidant reserve is improved larger can be a subgroup that is more likely to benefit symptoms, but subgroup interpretation remains problematic, and such improvements should be confirmed prospectively^{15,16}.

Surveys of oxidative stress biomarkers in coronary artery disease underscore the notion that MDA and

other lipid peroxidation products, antioxidant enzymes and glutathione-related pathways can be used to complement information on vascular injury and antioxidant capacity¹⁷.

The results also correspond to the antioxidant biology of melatonin which is known. Recent reviews define melatonin as a direct free-radical scavenger and an indirect modulator of antioxidant defense mechanisms, such as mitochondrial functional and redox-sensitive signaling pathways^{18,19}.

A large percentage of cardiovascular melatonin studies has been devoted to ischemia-reperfusion injury, cardioprotection, metabolic disease or perioperative oxidative stress instead of symptom change instable angina, which supports the rationale of large-scale prospective studies in this particular population²⁰.

The strengths of this research are that it is a randomized placebo-controlled parent study, repeated biomarker measurements, multiple oxidative stress markers, and a measure of clinically significant outcomes. It has weaknesses such as exploratory secondary-analysis

design, small sample, potential residual confounding, use of selected biomarkers as opposed to a redox panel, and lack of causality inference based on biomarker outcome correlations²¹.

CONCLUSION

Greater reduction in MDA and greater increase in GSH were linked with larger reductions in angina frequency, angina severity, nitrate use, and PSQI score, while SOD showed weaker but consistent associations.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Zahraa R. Hadi, Layth Jabbar
Drafting or Revising Critically:	Zahraa R. Hadi, Layth Jabbar
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

Conflict of Interest: The study has no conflict of interest to declare by any author.

Source of Funding: None

Ethical Approval: No. IQ.UTQ.PHARM.2025.005
Dated 19.01.2026

REFERENCES

- Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024;45(36):3415-37.
- Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease. *Circulation* 2023;148(9):e9-e119.
- Alkufi HK, Kareem AT, Hasan SA, Najem NA. Protective and therapeutic role of Ajwa date extract in propionic acid-induced autism in rats. *J. Anim. Health Prod* 2026;14(1):199-204.
- Abu-Elfotuh K, Abbas AN, Najm MA, Qasim QA, Hamdan AM, Abdelrehim AB, et al. Neuroprotective effects of punicalagin and/or micronized zeolite clinoptilolite on manganese-induced Parkinson's disease in a rat model: Involvement of multiple pathways. *CNS Neurosci Therapeutics* 2024;30(10):e70008.
- Hashim ZR, Qasim QA, ALabbod MH. The association of serum calcium and vitamin D with insulin resistance and beta-cell dysfunction among people with type 2 diabetes. *Arch Razi Inst* 2022; 77(5):1593.
- Zamanian MY, Golmohammadi M, Nili-Ahmadabadi A, Alameri AA, Al-Hassan M, Alshahrani SH, et al. Targeting autophagy with tamoxifen in breast cancer: From molecular mechanisms to targeted therapy. *Fundam Clin Pharmacol* 2023;37(6):1092-108.
- Qasim Q. Antioxidants, lipid profiles, and glucose levels, as well as persistent inflammation, are central to the link between diabetes mellitus type ii and oxidative stress. *Georgian Med News* 2024; 1(351):158-61.
- Hasan SA, Abass AA, Jabbar L. The protective role of ethanolic extract of ginseng (*Panax ginseng*) against adverse physiological and histological alterations in the liver of female rabbits exposed to chlorine. *Advancements Life Sci* 2025;12(1):185-90.
- Mohammadi N, Alizadeh M, Akbarzadeh S, Rezaei M, Mahmoodi M, Netticadan T, et al. Melatonin administered postoperatively lowers oxidative stress and inflammation and significantly recovers heart function in patients undergoing CABG surgery. *Eur J Med Res* 2025;30:585.
- Margiana R, HamoudAlshahrani S, Kayumova D, HussienRadieAlawadi A, Hjazi A, Alsalamy A, et al. Association between maternal exposure to arsenic by drinking water during pregnancy and risk of preterm birth: a systematic review and meta-analysis. *Int J Environ Health Res* 2024;34(8):2947-56.
- Huldani H, Malviya J, Rodrigues P, Hjazi A, Deorari MM, Al-Hetty HR, et al. Discovering the strength of immunometabolism in cancer therapy: employing metabolic pathways to enhance immune responses. *Cell Biochem Function* 2024;42(2):e3934.
- Qasim QA, Al-Salman HN. The isolation characterization and assessment of bioactive flavonoid with special reference to anti-arthritis activity. *Materials Today: Proceedings* 2023;80:2567-72.
- Medina-Leyte DJ, Zepeda-García O, Domínguez-Pérez M, González-Garrido A, Villarreal-Molina T, Jacobo-Albavera L. Endothelial dysfunction, inflammation and coronary artery disease: potential biomarkers and promising therapeutical approaches. *Front Cardiovasc Med* 2021;8:644442.
- Abd-Alrassol KS, Qasim QA, Al-Salman HN, Hussein HH. The spectrophotometric determination of antiepileptic drug in standard and pharmaceutical formulations by diazotization coupling reaction and some metals complexes. *Sys Rev Pharmacy* 2020;11(3).
- Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin: a pleiotropic, orchestrating regulator molecule. *Prog Neurobiol* 2011;93(3):350-84.
- Alshahrani SH, Alameri AA, Kahar F, Ramírez-Coronel AA, Obaid RF, Alsaikhan F, et al. Overview of the role and action mechanism of

- microRNA-128 in viral infections. *Microbial Pathogenesis* 2023;176:106020.
17. Ali RH, Hussein FK, Nasar DM, Abd Al salam Salem A. The relevance of mitochondrial DNA mutation in human diseases and forensic sciences. *Al-Nahrain J Sci* 2025;28(1):96-106.
 18. Al Alwan B, Alameri AA, Qasim QA, Vaqqosov S, Jawad Kadhim Z, Sivaraman R, et al. Evaluation of structural and thermodynamic parameters of dibenzothiophene desulfurization by carbon Nano-Filter. *Polycyclic Aromatic Compounds* 2023;43(9):8252-64.
 19. Jasim SA, Ramirez-Coronel AA, Alameri AA, Sapaev IB, Mustafa YF, Jalil AT, et al. Phenytoin drug detection study through the B24N24 and Al24N24 nano-clusters in gas and solvent phase: DFT, TD-DFT, and thermodynamic study. *Inorganic Chem Comm* 2023;153:110887.
 20. Yaprak M, Altun A, Vardar A, Aktoz M, Ciftci S, Ozbay G. Decreased nocturnal synthesis of melatonin in patients with coronary artery disease. *Int J Cardiol* 2003;89(1):103-7.
 21. Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;323(7321):1123-4.