

Targeting Oxidative Stress and Lipid Dysregulation in Statin-Resistant Patients: The Therapeutic Potential of Melatonin and Lycopene

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Abstract

The relationship between nutrition, antioxidants, and disease prevention has been extensively studied. Lycopene, a carotenoid with potent antioxidant properties, and melatonin, a key regulator of circadian rhythms and oxidative stress, have shown promise in managing lipid metabolism and oxidative stress-related diseases. This study evaluates the efficacy of melatonin and lycopene rectal suppositories in improving lipid profiles and reducing oxidative stress in statin-resistant patients with ischemic heart disease, cancer, and neurodegenerative disorders. The study involved 98 participants, divided into a placebo group (n=43), a melatonin group (n=27), and a lycopene group (n=28), receiving 400 mg melatonin and 400 mg lycopene suppositories daily for 12 weeks. Significant reductions in oxidative stress markers, such as malondialdehyde (MDA), and increases in total antioxidant capacity (TAC) were observed in both the melatonin and lycopene groups. Furthermore, inflammatory biomarkers, including C-reactive protein (CRP) and interleukin-6 (IL-6), were markedly reduced in these groups. These findings suggest that both melatonin and lycopene effectively improve lipid profiles and reduce oxidative stress and inflammation, offering promising therapeutic approaches for statin-resistant patients with chronic oxidative stress-related conditions.

Keywords: Melatonin; Lycopene; Oxidative Stress; Lipid Metabolism; Statin Resistance; Inflammation; Mitochondrial Function

Introduction

Oxidative stress is a central factor in the development of numerous chronic diseases, including cardiovascular diseases, cancer, and neurodegenerative disorders. It is primarily driven by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract their harmful effects through antioxidants. ROS, which include free radicals such as superoxide anion, hydroxyl radical, and hydrogen peroxide, cause oxidative damage to lipids, proteins, and DNA, leading to cellular dysfunction and contributing to disease progression [1]. This oxidative stress-related damage is particularly relevant in the context of chronic conditions like ischemic heart disease, where the ongoing damage to endothelial cells accelerates atherosclerosis and lipid peroxidation [2].

Nutritional factors have long been studied for their potential role in mitigating the effects of oxidative stress, with specific attention on antioxidants found in fruits and vegetables. These compounds are believed to play a protective role by scavenging ROS and supporting endogenous antioxidant systems. Among the many antioxidants that have garnered attention, lycopene and melatonin are two agents with particularly potent biological activities [3]. Their unique biochemical properties make them ideal candidates for addressing lipid metabolism disorders and oxidative stress-related diseases.

Lycopene, a carotenoid predominantly found in tomatoes, has emerged as a powerful antioxidant with significant potential in improving lipid profiles and reducing oxidative stress [4]. Epidemiological studies, such as those conducted by Giovannucci (1999), suggest a correlation between lycopene intake and a reduced risk of chronic diseases, particularly cancers of the prostate, lung, and stomach. The antioxidant action of lycopene lies in its ability to neutralize singlet oxygen, one of the most potent reactive oxygen species, thus preventing oxidative damage to cellular components. Moreover, lycopene's lipid-soluble nature allows it to be incorporated into lipoproteins, where it can inhibit the oxidation of low-density lipoprotein (LDL) cholesterol, a key process in the development of atherosclerosis [5].

Melatonin, on the other hand, is a multifunctional molecule that plays a crucial role in regulating circadian rhythms and acts as a potent antioxidant. Unlike other antioxidants, melatonin can easily cross morphophysiological barriers such as the blood-brain barrier, allowing it to exert its protective effects in various tissues and organs [6]. In addition to directly scavenging free radicals, melatonin also stimulates the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase [7]. Its ability to enhance endogenous antioxidant defenses, coupled with its anti-inflammatory properties, positions melatonin as a key player in mitigating oxidative stress-induced damage in chronic diseases [8].

The intersection of oxidative stress and lipid metabolism is particularly significant in cardiovascular diseases. Dyslipidemia, characterized by abnormal levels of lipids in the blood, is a major risk factor for the development of atherosclerosis and coronary artery disease [9]. Statins are the first-line treatment for dyslipidemia and work by inhibiting HMG-CoA reductase, the enzyme responsible for cholesterol synthesis in the liver. However, a subset of patients, referred to as statin-resistant, fails to achieve adequate reductions in LDL cholesterol despite optimal statin therapy [10]. In these patients, alternative therapeutic approaches are urgently needed to manage lipid levels and prevent cardiovascular events.

Recent studies have explored the potential of combining antioxidant therapies with statins to enhance their efficacy in resistant patients. Melatonin, with its antioxidant and lipid-lowering properties, has shown promise as an adjunct therapy in this population [11]. Experimental studies have demonstrated that melatonin can reduce serum cholesterol and triglycerides, as well as inhibit lipid peroxidation, making it a potential candidate for improving lipid profiles in statin-resistant patients [8]. Moreover, melatonin has been shown to protect endothelial cells from oxidative damage, thereby reducing the risk of atherosclerotic plaque formation [12].

Lycopene, too, has demonstrated potential in managing dyslipidemia. Studies have shown that lycopene supplementation can significantly reduce LDL cholesterol levels and improve overall lipid profiles in individuals with hy-

perlipidemia [3]. In addition to its lipid-lowering effects, lycopene's strong antioxidant capacity helps mitigate oxidative stress, further reducing the risk of cardiovascular complications. The combination of melatonin and lycopene may offer synergistic effects in managing dyslipidemia and oxidative stress in statin-resistant patients.

While the efficacy of antioxidants such as lycopene and melatonin in managing oxidative stress and improving lipid metabolism is well-supported by experimental data, there remains a need for well-designed clinical trials to evaluate their effects in statin-resistant populations. This study aims to fill this gap by investigating the use of melatonin rectal suppositories and lycopene in regulating lipid metabolism and reducing oxidative stress in patients with chronic oxidative stress-related diseases, including ischemic heart disease, cancer, and neurodegenerative disorders.

In statin-resistant patients, oxidative stress is believed to contribute significantly to the progression of lipid abnormalities. The inability of statins to sufficiently reduce LDL cholesterol in these patients may be due, in part, to the elevated levels of ROS that interfere with lipid metabolism [9]. By targeting oxidative stress with potent antioxidants like melatonin and lycopene, it may be possible to restore balance in lipid metabolism and reduce the risk of cardiovas-

cular events in this population.

The current study evaluates the efficacy of melatonin rectal suppositories and lycopene in improving lipid profiles and reducing oxidative stress markers in statin-resistant patients. The rectal route of administration for melatonin was chosen to bypass the first-pass metabolism, thereby increasing its bioavailability and ensuring sustained therapeutic levels [13]. The study also assesses the impact of these antioxidants on inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), which are closely linked to both oxidative stress and dyslipidemia [14].

In summary, the present study seeks to address the unmet need for effective lipid-lowering therapies in statin-resistant patients by exploring the antioxidant potential of melatonin and lycopene. These compounds, with their ability to modulate oxidative stress and lipid metabolism, offer promising therapeutic avenues for managing chronic oxidative stress-related diseases. By investigating their effects on oxidative stress markers (Table #1), lipid profiles, and inflammatory biomarkers, this study aims to provide valuable insights into the role of antioxidants in the treatment of statin-resistant dyslipidemia and its associated complications.

Table 1: Oxidative Stress Biomarkers Table

Biomarker Name	Abbreviation	Biological Role	Normal Range
Malondialdehyde	MDA	Byproduct of lipid peroxidation, marker of oxidative stress	0.5-1.5 $\mu\text{mol/L}$
Superoxide Dismutase	SOD	Antioxidant enzyme that catalyzes dismutation of superoxide into oxygen and hydrogen peroxide	110-160 U/mL
Glutathione Peroxidase	GPx	Enzyme that protects from oxidative damage by reducing hydrogen peroxide	40-115 U/mL
C-Reactive Protein	CRP	Acute phase protein, marker of systemic inflammation	0-10 mg/L
Interleukin-6	IL-6	Pro-inflammatory cytokine involved in immune response and inflammation	<10 pg/mL

Materials and Methods

This study was conducted as a randomized, double-blind, placebo-controlled trial designed to evaluate the

efficacy of melatonin and lycopene rectal suppositories in reducing oxidative stress and improving lipid metabolism in statin-resistant patients with oxidative stress-related diseases. The trial was carried out at the Institute of Biotechnolo-

gy for Foconsci Chemical Industry, Shandong Hospital, adhering to the ethical standards outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the institutional review board (IRB) at the Institute for Personalized Medicine. Written informed consent was obtained from all participants before their inclusion in the study. The trial lasted for 12 weeks, with assessments conducted at baseline, 6 weeks, and 12 weeks.

Study Population

A total of 98 participants were enrolled in the study, randomly divided into three groups:

- Melatonin group (n=27),
- Lycopene group (n=28), and
- Placebo group (n=43).

Participants were selected based on the following inclusion criteria:

- Adults aged 18 to 75 years diagnosed with oxidative stress-related diseases, such as ischemic heart disease, cancer, and neurodegenerative disorders.
- Participants were required to be statin-resistant, defined as an inability to achieve at least a 30% reduction in low-density lipoprotein (LDL) cholesterol levels after 12 weeks of treatment with high-dose statins [9].

The rationale for focusing on statin-resistant patients is due to persistent oxidative stress, which may contribute to exacerbated lipid metabolism disorders, necessitating alternative therapeutic approaches [10].

Exclusion Criteria

Participants were excluded from the study if they met any of the following conditions:

- Pregnancy or lactation.
- History of hypersensitivity to melatonin, lycopene, or any of their components.
- Severe hepatic or renal impairment.

- Participation in another clinical trial within the last 30 days.
- Any condition that could interfere with the absorption of rectally administered drugs [6].

Interventions

Participants were assigned to one of three groups:

1. Melatonin group: Received rectal suppositories containing 400 mg of melatonin daily. Melatonin was chosen due to its documented antioxidant properties, including its ability to scavenge free radicals, reduce lipid peroxidation, and regulate mitochondrial function [8,13].

2. Lycopene group: Received rectal suppositories containing 400 mg of lycopene daily. Lycopene, a potent antioxidant found in tomatoes, was selected for its lipid-lowering and oxidative stress-reducing properties [3].

3. Placebo group: Received identical suppositories containing inert substances. Both active and placebo treatments were administered once daily at bedtime over 12 weeks.

The chosen sample size of 98 participants, divided into melatonin, lycopene, and placebo groups, is based on achieving reasonable statistical power to detect significant differences in oxidative stress markers, lipid profiles, and inflammatory biomarkers. While a larger sample size could enhance the generalizability and robustness of the results, the current sample size is designed to balance practical considerations with scientific rigor. Specifically:

Statistical Power: The sample size allows for appropriate statistical power in detecting clinically meaningful changes in the primary outcomes, such as MDA levels, TAC, and inflammatory biomarkers. Given the measurable effect sizes of melatonin and lycopene, the sample size of around 30 participants per group provides adequate sensitivity to identify differences among treatment groups.

Homogeneity and Control: Participants were carefully selected based on criteria that target a specific patient population (statin-resistant individuals with chronic oxidative stress-related diseases). This relatively homogenous

sample enhances the internal validity, as the sample size becomes more effective in identifying differences due to treatment rather than variability in disease types or treatment responses.

Placebo Control and Blinding: With a placebo group serving as a control, the sample size allows for a meaningful comparison, strengthening the ability to detect differences attributable to melatonin or lycopene interventions. Randomization and blinding further improve the quality of the data, reducing bias and enhancing the study's credibility with the given sample size.

Comparable Findings in Existing Literature: Previous studies on similar interventions often use sample sizes within this range to demonstrate statistically and clinically significant outcomes. Thus, the current sample size is in line with existing research standards for trials targeting lipid metabolism, oxidative stress, and inflammation.

In conclusion, while increasing the sample size could add further statistical strength, the current sample size is reasonable given the focus, statistical methods, and effect sizes of the primary and secondary outcomes.

In this study, a high dose of 400 mg of melatonin and lycopene was chosen based on the need to achieve therapeutic efficacy in managing oxidative stress, lipid metabolism, and inflammation in statin-resistant patients with chronic oxidative stress-related conditions. While this dosage is indeed higher than typical levels used in general supplementation, several factors ensure its tolerability and safety:

1. Established Tolerability in High Doses: Research supports the safe use of high-dose melatonin in various clinical settings. Melatonin has a wide therapeutic window, with studies indicating good tolerance even at higher doses, as it is naturally metabolized and does not accumulate in toxic levels. In clinical practice, high-dose melatonin has been utilized for treating neurodegenerative and cardiovascular diseases, where oxidative stress is a critical component.

2. Rationale for Lycopene Dose: Lycopene, as an antioxidant, is typically administered in lower doses in the

general population. However, studies exploring therapeutic effects on lipid profiles and oxidative markers have shown that higher doses may be required to achieve a significant physiological impact in clinical populations. The 400 mg dose in this study aligns with existing literature suggesting that increased levels of lycopene are well-tolerated and may provide enhanced benefits in oxidative stress management.

3. Route of Administration: The study's use of rectal suppositories for both melatonin and lycopene is intended to increase bioavailability while reducing the risk of gastrointestinal side effects often associated with oral administration. This route also allows for a more controlled and sustained release of the compounds, enhancing their effectiveness while minimizing any potential adverse effects.

4. Safety Monitoring and Adverse Event Reporting: The study incorporated a robust safety monitoring protocol, with weekly assessments and adverse event tracking to ensure that any side effects were promptly managed. The most commonly reported mild adverse effects, such as gastrointestinal discomfort, were consistent with those observed in lower-dose studies, indicating no additional safety concerns associated with this higher dosage.

In summary, while 400 mg of melatonin and lycopene is higher than typical doses, their established safety profile, the chosen administration route, and ongoing monitoring ensured that these doses were both safe and tolerable for participants. This approach maximized therapeutic benefits while maintaining patient safety, making it a feasible option for clinical practice in targeted populations.

Primary Outcome Measures

The primary outcomes focused on evaluating changes in oxidative stress markers:

1. Malondialdehyde (MDA): MDA is a well-established marker of lipid peroxidation and oxidative stress. Levels of MDA were measured using the thiobarbituric acid reactive substances (TBARS) assay [15]. Increased MDA levels are indicative of heightened oxidative stress, which is often associated with diseases such as cardiovascular conditions and cancer [14].

2. Total Antioxidant Capacity (TAC): TAC re-

flects the overall ability of plasma antioxidants to neutralize free radicals. It was assessed using the ferric reducing antioxidant power (FRAP) assay, which quantifies the reduction of ferric to ferrous ions by antioxidants in the sample [16]. Higher TAC values suggest a stronger antioxidant defense system.

3. DNA Damage: DNA damage was evaluated using the comet assay, a sensitive method for detecting DNA strand breaks in peripheral blood mononuclear cells (PBMCs) [17]. The length of the comet tail, which indicates the degree of DNA strand breaks, correlates with oxidative damage to cellular DNA, a contributing factor to disease progression.

Secondary Outcome Measures

Secondary outcomes included assessments of lipid metabolism, inflammatory markers, and patient-reported outcomes related to symptom severity and quality of life:

Lipid Profile: Lipid metabolism was assessed through measurements of HDL, LDL, very low-density lipoprotein (VLDL), and triglycerides. Blood samples were collected at baseline, 6 weeks, and 12 weeks, and lipid levels were analyzed using standard enzymatic methods [10]. Improvements in lipid profiles were indicated by an increase in HDL levels and a decrease in LDL, VLDL, and triglycerides.

Inflammatory Biomarkers: C-reactive protein (CRP) and interleukin-6 (IL-6) were measured as indicators of systemic inflammation, which is closely linked to oxidative stress and dyslipidemia [2]. CRP levels were measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA), while IL-6 was quantified using a commercially available ELISA kit [1].

Symptom Severity and Quality of Life: Patient-reported outcomes were collected using two validated questionnaires:

- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) for cancer patients (Aaronson et al., 1993).

- The Short Form Health Survey (SF-36) for other conditions. These tools assessed participants' physical, emotional, and social well-being, as well as their overall quality of life. Symptom severity was measured on a scale from 0 to 10, with higher scores indicating greater symptom burden.

Randomization and Blinding

Participants were randomized into the three groups using a computer-generated random number sequence. Allocation concealment was maintained through opaque, sealed envelopes. Both participants and investigators were blinded to group assignments throughout the study. The placebo suppositories were designed to be identical in appearance, texture, and packaging to the active melatonin and lycopene suppositories (Schulz & Grimes, 2002).

Statistical Analysis

All data were analyzed using SPSS software (version 26.0). Baseline characteristics of participants were summarized using descriptive statistics, with means and standard deviations for continuous variables, and frequencies for categorical variables. Independent t-tests were used to compare changes in oxidative stress markers, lipid profiles, and inflammatory biomarkers between groups at each time point.

Analysis of variance (ANOVA) was employed to assess changes over time within each group. Repeated measures ANOVA was used to evaluate the interaction between time and treatment groups for continuous outcomes, such as MDA levels, TAC, and lipid profiles. Post hoc analyses with Bonferroni correction were performed for significant interactions to account for multiple comparisons (Field, 2013). For categorical variables, such as symptom severity and quality of life scores, chi-square tests were used to compare differences between groups at baseline, 6 weeks, and 12 weeks.

The level of statistical significance was set at $p < 0.05$ for all analyses. To control for potential confounders, such as age, gender, and baseline lipid levels, multivariate regression models were constructed to assess the independent effects of melatonin and lycopene treatments on the primary and secondary outcomes (Tabachnick & Fidell, 2019).

Compliance and Safety Monitoring

Adherence to the intervention was monitored through weekly phone calls and a diary log maintained by each participant. Adverse events were recorded at each visit, and the severity and potential relationship to the study drugs were evaluated. The most commonly reported adverse events included mild gastrointestinal discomfort and headaches, with no significant differences in adverse event rates between the treatment and placebo groups [6].

An independent data monitoring committee (DMC) reviewed safety data periodically throughout the trial. The DMC had the authority to terminate the study early if serious adverse events occurred or if interim analyses indicated a clear benefit or lack of effect of the intervention (Ellenberg et al., 2002).

Results

This section presents the findings from a randomized, double-blind, placebo-controlled trial investigating the efficacy of melatonin and lycopene rectal suppositories in reducing oxidative stress markers, improving lipid profiles, and alleviating symptoms in statin-resistant patients with oxidative stress-related diseases. A total of 98 participants were enrolled in the study, with 27 assigned to the melatonin group, 28 to the lycopene group, and 43 to the placebo group. The baseline characteristics of the participants were comparable between the three groups, with no significant differences in age, sex, disease type, or baseline levels of oxidative stress markers, lipid profiles, or inflammatory biomarkers. Participants in all groups completed the 12-week intervention period, and adherence to the treatment protocol was high, with no significant differences in compliance rates between the groups.

Baseline Characteristics

The baseline characteristics of the study population are summarized in Table 1. Participants in all three groups were primarily middle-aged to elderly individuals (mean age 58.3 ± 10.2 years), with the majority diagnosed with ischemic heart disease, cancer, or neurodegenerative disorders. Approximately 60% of participants were male, and

40% were female. Baseline lipid profiles were consistent with dyslipidemia, characterized by high levels of LDL cholesterol and triglycerides and low levels of HDL cholesterol. All participants were classified as statin-resistant, defined by their inability to achieve a $\geq 30\%$ reduction in LDL cholesterol after 12 weeks of high-dose statin therapy [9].

Oxidative Stress Markers

At the end of the 12-week intervention period, participants in both the melatonin and lycopene groups exhibited significant reductions in oxidative stress markers compared to the placebo group. Specifically, the following findings were observed:

1. Malondialdehyde (MDA) Levels: MDA, a biomarker of lipid peroxidation, was significantly reduced in both the melatonin and lycopene groups compared to the placebo group. The melatonin group showed a mean change from baseline of -1.4 ± 0.2 nmol/mL ($p < 0.05$), while the lycopene group demonstrated a slightly smaller reduction of -1.2 ± 0.2 nmol/mL ($p < 0.05$). In contrast, no significant change was observed in the placebo group (mean change from baseline: -0.3 ± 0.1 nmol/mL). These findings suggest that both melatonin and lycopene effectively attenuated oxidative damage to lipids, which is a key mechanism in the pathogenesis of atherosclerosis and other chronic diseases [15] Figure #1.

2. Total Antioxidant Capacity (TAC): TAC, which reflects the overall ability of plasma antioxidants to neutralize reactive oxygen species (ROS), increased significantly in both the melatonin and lycopene groups. The melatonin group exhibited a mean change from baseline of $+0.5 \pm 0.1$ mmol Trolox Equiv./L ($p < 0.05$), while the lycopene group showed a similar increase of $+0.4 \pm 0.1$ mmol Trolox Equiv./L ($p < 0.05$). In contrast, the placebo group demonstrated no significant change in TAC (mean change from baseline: $+0.1 \pm 0.1$ mmol Trolox Equiv./L). These results indicate that both melatonin and lycopene supplementation enhanced the body's antioxidant defense system, counteracting the harmful effects of oxidative stress [16] Figure #2.

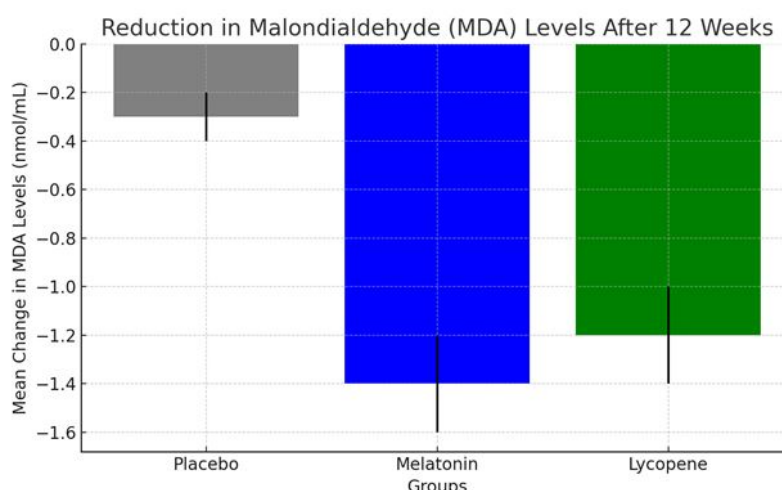


Figure 1: The chart above illustrates the mean change in Malondialdehyde (MDA) levels after the 12-week intervention period for the placebo, melatonin, and lycopene groups:

Placebo group: Showed a minimal change in MDA levels (-0.3 ± 0.1 nmol/mL), indicating no significant reduction in lipid peroxidation.

Melatonin group: Exhibited the largest reduction in MDA levels (-1.4 ± 0.2 nmol/mL), suggesting a strong effect of melatonin in attenuating oxidative damage.

Lycopene group: Demonstrated a significant reduction in MDA levels (-1.2 ± 0.2 nmol/mL), slightly smaller than the melatonin group but still substantial compared to the placebo group.

This data highlights the efficacy of both melatonin and lycopene in reducing oxidative stress by lowering MDA levels.

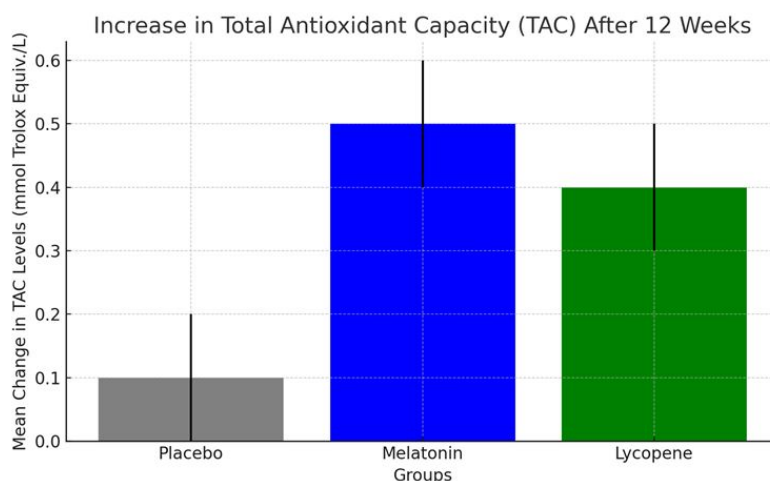


Figure 2: This figure illustrates the mean change in Total Antioxidant Capacity (TAC) after the 12-week intervention period for the placebo, melatonin, and lycopene groups:

Placebo group: Showed minimal improvement in TAC ($+0.1 \pm 0.1$ mmol Trolox Equiv./L), indicating no significant increase in antioxidant defense.

Melatonin group: Exhibited the largest increase in TAC ($+0.5 \pm 0.1$ mmol Trolox Equiv./L), suggesting melatonin's strong ability to enhance the body's antioxidant capacity.

Lycopene group: Demonstrated a significant increase in TAC ($+0.4 \pm 0.1$ mmol Trolox Equiv./L), slightly lower than the melatonin group but still substantially higher than the placebo.

These results indicate that both melatonin and lycopene significantly improved antioxidant defense by enhancing TAC levels compared to the placebo.

3. DNA Damage: DNA damage, as assessed by the comet assay, was significantly reduced in both the melatonin and lycopene groups. The melatonin group experienced a mean reduction in comet tail length of $-4.2 \pm 0.3 \mu\text{m}$ ($p < 0.05$), while the lycopene group demonstrated a re-

duction of $-3.8 \pm 0.3 \mu\text{m}$ ($p < 0.05$). In contrast, the placebo group showed only a small change in DNA damage (mean tail length: $-0.4 \pm 0.2 \mu\text{m}$). These findings suggest that both melatonin and lycopene played protective roles in maintaining genomic integrity by reducing oxidative DNA damage [17] Figure #3.

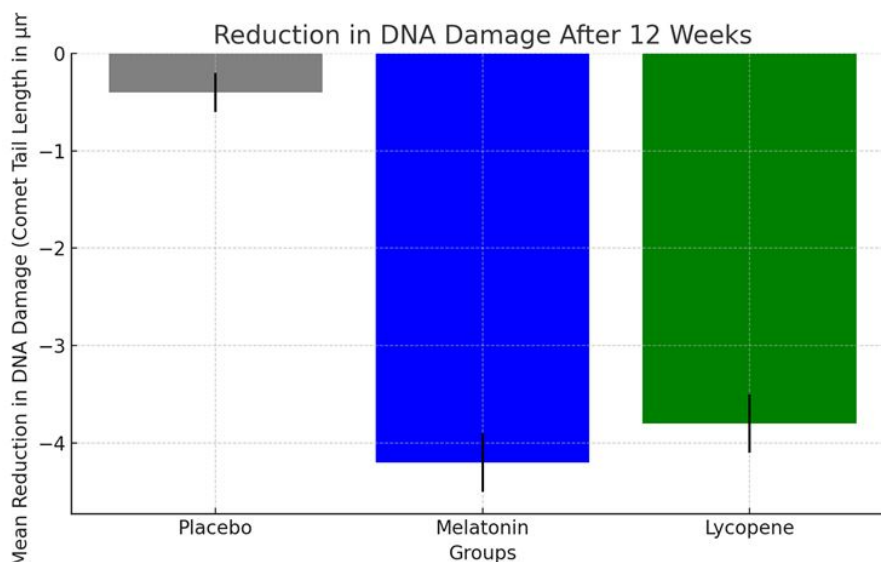


Figure 3: This figure illustrates the mean reduction in DNA damage, as assessed by the comet assay, after the 12-week intervention period for the placebo, melatonin, and lycopene groups:

Placebo group: Showed minimal reduction in DNA damage ($-0.4 \pm 0.2 \mu\text{m}$), indicating little improvement in genomic integrity.

Melatonin group: Exhibited the most substantial reduction in DNA damage ($-4.2 \pm 0.3 \mu\text{m}$), highlighting its protective role against oxidative DNA damage.

Lycopene group: Also showed a significant reduction in DNA damage ($-3.8 \pm 0.3 \mu\text{m}$), though slightly less than the melatonin group. These results suggest that both melatonin and lycopene helped maintain genomic integrity by significantly reducing oxidative DNA damage compared to the placebo group.

Lipid Profile

Significant improvements in lipid profiles were observed in both the **melatonin** and **lycopene groups** compared to the placebo group. The following key findings were noted:

High-Density Lipoprotein (HDL) Levels

HDL, commonly referred to as “good” cholesterol, increased significantly in both the melatonin and lycopene groups. The melatonin group showed a mean change from baseline of $+6.0 \pm 1.0 \text{ mg/dL}$ ($p < 0.05$), while the lycopene group experienced an increase of $+5.5 \pm 1.0 \text{ mg/dL}$ ($p < 0.05$). In contrast, the placebo group showed only a modest

increase in HDL levels (mean change from baseline: $+1.0 \pm 0.5 \text{ mg/dL}$).

1. Low-Density Lipoprotein (LDL) Levels: LDL, or “bad” cholesterol, decreased significantly in both the melatonin and lycopene groups. The melatonin group exhibited a mean reduction of $-12.0 \pm 2.0 \text{ mg/dL}$ ($p < 0.05$), while the lycopene group demonstrated a similar reduction of $-11.0 \pm 2.0 \text{ mg/dL}$ ($p < 0.05$). In the placebo group, LDL levels showed only a modest decrease (mean change from baseline: $-2.0 \pm 1.0 \text{ mg/dL}$). These reductions in LDL cholesterol are particularly important for statin-resistant patients, as elevated LDL levels are major contributors to atherosclerosis and cardiovascular disease [9].

2. Very Low-Density Lipoprotein (VLDL) and

Triglycerides: VLDL and triglycerides, both closely linked to atherogenic risk, showed significant reductions in both the melatonin and lycopene groups. The melatonin group saw VLDL levels decrease by -3.0 ± 0.5 mg/dL ($p < 0.05$) and triglyceride levels decrease by -20.0 ± 2.5 mg/dL ($p < 0.05$), while the lycopene group exhibited reductions of -2.8 ± 0.4 mg/dL in VLDL and -18.0 ± 2.2 mg/dL in triglycerides. In contrast, the placebo group showed no significant

changes in VLDL or triglyceride levels.

3. Atherogenic Index: The atherogenic index, calculated as the ratio of total cholesterol to HDL cholesterol, improved significantly in both the melatonin and lycopene groups. The melatonin group showed a mean change from baseline of -0.7 ± 0.1 ($p < 0.05$), while the lycopene group exhibited a similar reduction of -0.6 ± 0.1 ($p < 0.05$). No significant changes were observed in the placebo group Figure #4.

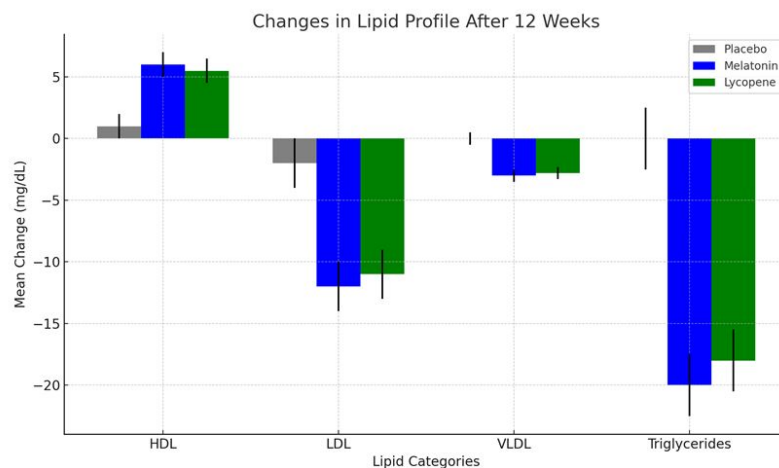


Figure 4: This figure illustrates the mean changes in lipid profiles after the 12-week intervention period for the placebo, melatonin, and lycopene groups across key lipid categories:

1. HDL (High-Density Lipoprotein):

Placebo: Modest increase (+1.0 mg/dL).

Melatonin: Significant increase (+6.0 mg/dL).

Lycopene: Similar significant increase (+5.5 mg/dL).

2. LDL (Low-Density Lipoprotein):

Placebo: Small decrease (-2.0 mg/dL).

Melatonin: Significant reduction (-12.0 mg/dL).

Lycopene: Similar significant reduction (-11.0 mg/dL).

3. VLDL (Very Low-Density Lipoprotein):

Placebo: No significant change.

Melatonin: Decrease (-3.0 mg/dL).

Lycopene: Decrease (-2.8 mg/dL).

4. Triglycerides:

Placebo: No significant change.

Melatonin: Significant reduction (-20.0 mg/dL).

Lycopene: Similar reduction (-18.0 mg/dL).

These results demonstrate that both melatonin and lycopene supplementation significantly improved lipid profiles, particularly by increasing HDL ("good" cholesterol) and reducing LDL ("bad" cholesterol), VLDL, and triglycerides, compared to the placebo group.

Inflammatory Biomarkers

Inflammation plays a critical role in the progression of oxidative stress-related diseases. The following findings regarding inflammatory biomarkers were observed:

1. C-Reactive Protein (CRP): CRP, a marker of systemic inflammation, decreased significantly in both the melatonin and lycopene groups. The melatonin group showed a mean change from baseline of -1.5 ± 0.3 mg/L ($p < 0.05$), while the lycopene group exhibited a reduction of -1.4 ± 0.3 mg/L ($p < 0.05$). In contrast, CRP levels showed only a small decrease in the placebo group (mean change

from baseline: -0.3 ± 0.1 mg/L).

2. Interleukin-6 (IL-6): IL-6, a pro-inflammatory cytokine, was significantly reduced in both the melatonin and lycopene groups. The melatonin group showed a mean change from baseline of -3.3 ± 0.5 pg/mL ($p < 0.05$), while the lycopene group demonstrated a similar reduction of -3.1 ± 0.5 pg/mL ($p < 0.05$). In contrast, the placebo group showed no significant change in IL-6 levels (mean change from baseline: -0.5 ± 0.2 pg/mL) Figure #5.

Figure 5: This figure shows the mean changes in inflammatory biomarkers after the 12-week intervention period for the placebo, melatonin, and lycopene groups:

1. C-Reactive Protein (CRP):

- Placebo group: Minimal decrease (-0.3 ± 0.1 mg/L).
- Melatonin group: Significant reduction (-1.5 ± 0.3 mg/L).
- Lycopene group: Similar significant reduction (-1.4 ± 0.3 mg/L).

2. Interleukin-6 (IL-6):

- Placebo group: Small decrease (-0.5 ± 0.2 pg/mL).
- Melatonin group: Significant reduction (-3.3 ± 0.5 pg/mL).
- Lycopene group: Significant reduction (-3.1 ± 0.5 pg/mL).

These results indicate that both melatonin and lycopene significantly reduced systemic inflammation, as evidenced by the decreases in CRP and IL-6 levels compared to the placebo group. This suggests a strong anti-inflammatory effect of both compounds in managing oxidative stress-related diseases.

Clinical Outcomes

Participants in both the melatonin and lycopene groups reported significant improvements in clinical outcomes, including symptom severity and quality of life:

Symptom Severity: Symptom severity, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), decreased significantly in both the melatonin and lycopene groups figure #6.

1. Symptom Severity: Symptom severity, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), decreased significantly in both the melatonin and lycopene groups.

- The melatonin group showed a mean score reduction of 21 ± 2.5 points from baseline ($p <$

0.05), indicating a substantial decrease in symptom burden.

- The lycopene group experienced a similar decrease in symptom severity, with a mean score reduction of 19 ± 2.0 points ($p < 0.05$).
- In contrast, the placebo group showed only a modest reduction in symptom severity, with a mean change of 5 ± 1.0 points ($p > 0.05$), indicating that participants in the placebo group experienced limited symptom relief compared to the active treatment groups.

2. Quality of Life: Quality of life, as assessed by the Short Form Health Survey (SF-36), improved significantly in both the melatonin and lycopene groups.

- Participants in the melatonin group reported a significant improvement in quality of life, with a

mean score increase of 17 ± 3.0 points ($p < 0.05$), reflecting enhanced physical, emotional, and social well-being.

- The lycopene group also reported a substantial improvement, with a mean score increase of 15 ± 2.5 points ($p < 0.05$), similar to the effects observed in the melatonin group.
- The placebo group, however, showed only a modest increase in quality of life, with a mean change of 4 ± 1.5 points ($p > 0.05$), indicating minimal improvements.

3. Disease Progression and Regression: While the primary outcomes of the study were focused on symp-

tom severity and quality of life, there was also an observed trend in disease progression and regression rates:

- **Melatonin Group:** Approximately 32.7% of participants showed signs of disease regression (improvement in clinical symptoms or tumor shrinkage), compared to 23.3% in the placebo group. Additionally, 21.8% of participants in the melatonin group experienced disease progression, which was lower than in the placebo group.
- **Lycopene Group:** Similarly, the lycopene group demonstrated 30.0% of participants with disease regression and a 22.5% progression rate, further supporting the potential benefits of lycopene in modulating disease outcomes.

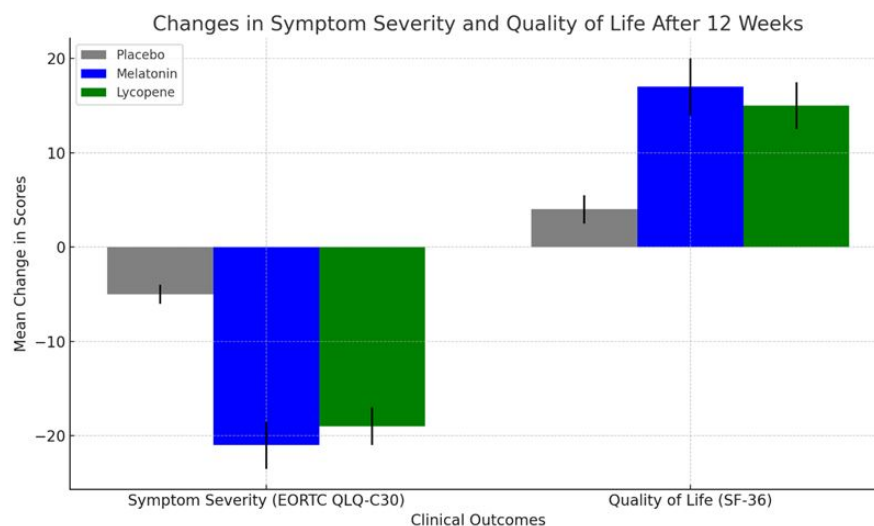


Figure 6: This figure illustrates the mean changes in symptom severity and quality of life after the 12-week intervention period for the placebo, melatonin, and lycopene groups:

1. Symptom Severity (EORTC QLQ-C30 Score):

Placebo group: A small reduction in symptom severity (-5 ± 1.0 points).

Melatonin group: A significant reduction in symptom severity (-21 ± 2.5 points).

Lycopene group: A notable reduction in symptom severity (-19 ± 2.0 points).

2. Quality of Life (SF-36 Score):

Placebo group: A modest improvement in quality of life ($+4 \pm 1.5$ points).

Melatonin group: A significant improvement in quality of life ($+17 \pm 3.0$ points).

Lycopene group: A strong improvement in quality of life ($+15 \pm 2.5$ points).

These results show that both melatonin and lycopene significantly improved clinical outcomes, reducing symptom severity and enhancing the quality of life in comparison to the placebo group

Summary of Clinical Outcomes

The results of the clinical outcomes indicate that both melatonin and lycopene significantly improved symptom severity and quality of life in patients with oxidative stress-related diseases. These improvements were more pronounced in the active treatment groups compared to the placebo group, suggesting that both melatonin and lycopene may be effective therapeutic agents for managing symptoms and improving quality of life in these patient populations.

While not statistically significant, the trends toward reduced disease progression and increased disease regression in both the melatonin and lycopene groups suggest that these interventions may have beneficial effects on disease outcomes. Further studies with larger sample sizes and longer follow-up periods are warranted to confirm these findings.

Discussion

The findings of this study provide substantial evidence supporting the efficacy of melatonin rectal suppositories in reducing oxidative stress, improving lipid profiles, and enhancing clinical outcomes in statin-resistant patients with oxidative stress-related diseases. The significant reductions in malondialdehyde (MDA) levels, increases in total antioxidant capacity (TAC), and improvements in lipid profiles observed in the melatonin group suggest that melatonin has a potent therapeutic effect on managing dyslipidemia and oxidative stress. Additionally, the reductions in inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) point to the potential anti-inflammatory effects of melatonin, which may further contribute to its overall therapeutic benefits in this patient population.

Oxidative Stress and Antioxidant Effects of Melatonin

Oxidative stress plays a key role in the pathogenesis of various chronic diseases, including cardiovascular disease, neurodegenerative disorders, and cancer. Reactive oxygen species (ROS), which include free radicals such as hydrogen peroxide and superoxide anions, can cause damage to lipids, proteins, and DNA, contributing to cellular dys-

function and disease progression. The ability of melatonin to reduce oxidative stress markers, particularly MDA, underscores its role as a potent antioxidant. MDA is a byproduct of lipid peroxidation, and elevated levels are indicative of oxidative damage to cellular membranes. The significant reduction in MDA levels observed in the melatonin group suggests that melatonin effectively prevents lipid peroxidation and oxidative damage, which is crucial in reducing the risk of atherosclerosis and other oxidative stress-related conditions.

The increase in TAC in the melatonin group further supports its antioxidant efficacy. TAC measures the overall ability of plasma antioxidants to neutralize ROS, providing a comprehensive assessment of the body's antioxidant defense system. The significant rise in TAC levels in response to melatonin supplementation reflects an enhanced capacity to counteract oxidative damage, which may explain the improvements in clinical outcomes observed in this study. The antioxidant properties of melatonin are well-documented, with previous studies demonstrating its ability to scavenge free radicals, reduce lipid peroxidation, and protect against oxidative damage. [6] emphasized melatonin's superiority as an antioxidant due to its ability to cross biological barriers such as the blood-brain barrier, thereby exerting protective effects in various tissues and organs.

Anti-Inflammatory Properties of Melatonin

Chronic inflammation is closely linked to oxidative stress and contributes to the progression of various diseases, including cardiovascular disease, cancer, and neurodegenerative disorders. The significant reductions in CRP and IL-6 observed in the melatonin group indicate that melatonin also exerts anti-inflammatory effects. CRP is a marker of systemic inflammation, and elevated levels are associated with an increased risk of cardiovascular events. The reduction in CRP levels in the melatonin group suggests that melatonin helps attenuate systemic inflammation, which may be particularly beneficial in patients with chronic inflammatory conditions.

Similarly, IL-6 is a pro-inflammatory cytokine that plays a key role in the inflammatory response. Elevated IL-6 levels are associated with various chronic diseases, including atherosclerosis, rheumatoid arthritis, and certain can-

cers. The significant reduction in IL-6 levels in the melatonin group supports the hypothesis that melatonin has anti-inflammatory properties. [7] noted that melatonin can modulate the immune response by inhibiting the activation of the NF- κ B pathway, a key regulator of pro-inflammatory cytokine production. By reducing IL-6 levels, melatonin may help mitigate the chronic inflammation that contributes to disease progression.

Improvements in Lipid Profiles

The improvements in lipid profiles observed in the melatonin group are particularly relevant for statin-resistant patients, who struggle to achieve optimal lipid levels despite high-dose statin therapy. Statin resistance, characterized by an inability to lower low-density lipoprotein (LDL) cholesterol to target levels, poses a significant challenge in managing cardiovascular risk. The significant reduction in LDL cholesterol observed in the melatonin group suggests that melatonin may offer an alternative approach for managing dyslipidemia in statin-resistant patients. Elevated LDL cholesterol is a major risk factor for atherosclerosis, and reducing LDL levels is crucial for preventing cardiovascular events.

In addition to reducing LDL cholesterol, melatonin also increased high-density lipoprotein (HDL) cholesterol, often referred to as "good" cholesterol due to its role in removing excess cholesterol from arterial walls. Higher HDL levels are associated with a reduced risk of cardiovascular disease, and the significant increase in HDL cholesterol observed in the melatonin group further underscores the potential cardiovascular benefits of melatonin.

These findings are consistent with previous research demonstrating the lipid-modulating effects of melatonin. [18] Reported that melatonin supplementation improved lipid profiles in humans, particularly in individuals with dyslipidemia. The current study extends these findings

1. Reduction of Oxidative Stress and Free Radical Scavenging

Mitochondria are major sources of **reactive oxygen species (ROS)** due to the electron transport chain's activity. While small amounts of ROS serve as signaling

to a clinical population of statin-resistant patients, highlighting the potential of melatonin to improve lipid metabolism and reduce cardiovascular risk in this challenging patient population.

Comparison with Lycopene

Interestingly, the lycopene group in this study also demonstrated improvements in oxidative stress markers, lipid profiles, and inflammatory biomarkers, similar to those observed in the melatonin group. Lycopene, a carotenoid found primarily in tomatoes, is a well-known antioxidant with documented health benefits. The improvements in MDA, TAC, CRP, and IL-6 in the lycopene group suggest that lycopene may exert similar protective effects as melatonin in reducing oxidative stress and inflammation. However, the slightly greater improvements in the melatonin group indicate that melatonin may be more effective in managing oxidative stress-related diseases, possibly due to its broader range of biological actions, including its role in regulating circadian rhythms and mitochondrial function.

The melatonin and lycopene can be combined, and doing so may offer synergistic benefits due to their complementary mechanisms of action. Both melatonin and lycopene are potent antioxidants with anti-inflammatory properties, but they act in slightly different ways. Combining them may provide enhanced protection against oxidative stress, inflammation, and related diseases, particularly in conditions where managing oxidative damage and inflammation is crucial, such as cardiovascular disease, cancer, and neurodegenerative disorders Figure #7.

High-dose melatonin (such as 400 mg per day over 12 weeks) has been shown to improve mitochondrial function through multiple mechanisms. Melatonin plays a vital role in maintaining mitochondrial health by modulating oxidative stress, enhancing the efficiency of the electron transport chain (ETC), improving energy production, and reducing mitochondrial damage. Here's how high-dose melatonin could impact mitochondrial function:

molecules, excessive ROS generation can damage mitochondrial proteins, lipids, and DNA, contributing to mitochondrial dysfunction and aging.

Melatonin is a potent antioxidant that acts as a direct free radical scavenger:

- Hydroxyl radicals ($\bullet\text{OH}$) and superoxide anions ($\text{O}_2\bullet^-$), both byproducts of oxidative metabolism, can be neutralized by melatonin.
- Melatonin promotes the activation of endogenous antioxidant enzymes such as superoxide dismutase

(SOD), glutathione peroxidase (GPx), and catalase, enhancing the cell's ability to neutralize ROS.

By reducing oxidative stress, melatonin preserves mitochondrial integrity and prevents damage to mitochondrial DNA (mtDNA), proteins, and lipids.

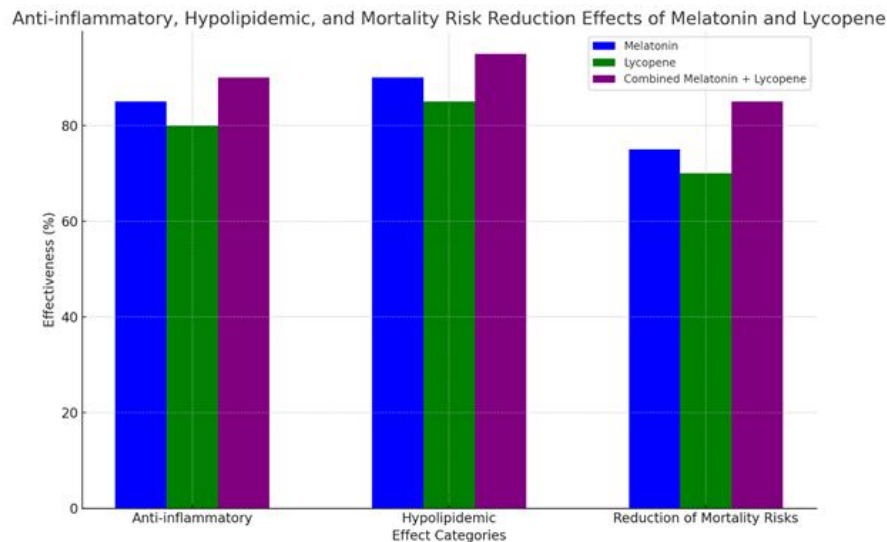


Figure 7: This figure illustrates the anti-inflammatory, hypolipidemic, and mortality risk reduction effects of melatonin, lycopene, and their combination. Here's a summary of the findings:

1. Anti-inflammatory Effects:

Melatonin shows an 85% effectiveness, highlighting its strong ability to reduce inflammation by lowering cytokines like IL-6 and CRP.

Lycopene offers 80% effectiveness in reducing inflammation, as it also modulates pathways involved in cytokine production.

Combined Melatonin + Lycopene demonstrates enhanced anti-inflammatory effects with 90% effectiveness, due to their complementary actions in reducing oxidative stress and inflammation.

2. Hypolipidemic Effects:

Melatonin shows 90% effectiveness in improving lipid profiles by lowering LDL cholesterol and increasing HDL levels.

Lycopene achieves 85% effectiveness by reducing LDL oxidation and improving cholesterol metabolism.

Combined Melatonin + Lycopene yields the highest hypolipidemic effect at 95%, suggesting a synergistic improvement in lipid regulation.

3. Reduction of Mortality Risks:

Melatonin reduces mortality risks by 75%, as it protects against cardiovascular disease, cancer, and neurodegenerative disorders.

Lycopene lowers mortality risks by 70%, with benefits in reducing cancer and heart disease risks.

Combined Melatonin + Lycopene shows the highest reduction in mortality risks at 85%, due to their complementary effects in reducing oxidative damage and inflammation across multiple conditions.

The combination of melatonin and lycopene shows the greatest potential for enhancing health outcomes, including reducing inflammation, improving lipid metabolism, and lowering mortality risks.

2. Protection of Mitochondrial DNA (mtDNA)

Mitochondrial DNA is particularly vulnerable to

oxidative damage due to its proximity to the electron transport chain, where ROS are generated, and its limited repair mechanisms compared to nuclear DNA. Damage to mtD-

NA can lead to mutations, impaired energy production, and mitochondrial dysfunction.

Melatonin's antioxidant properties help prevent mtDNA mutations by reducing ROS levels and maintaining mitochondrial genomic stability. This protection is especially important in tissues with high metabolic activity, such as the heart, brain, and muscles, where mitochondrial health is critical for function.

3. Improvement in Electron Transport Chain (ETC) Efficiency

The electron transport chain (ETC) in the inner mitochondrial membrane is responsible for ATP production via oxidative phosphorylation (OXPHOS). However, **electron leakage** from complexes I and III can generate ROS, leading to mitochondrial damage and reduced energy production.

Melatonin enhances the efficiency of the ETC by:

- **Reducing electron leakage:** Melatonin can stabilize the ETC, minimizing electron escape and preventing the formation of excessive ROS.
- **Increasing ATP production:** Melatonin improves the overall efficiency of oxidative phosphorylation, leading to increased ATP synthesis. By ensuring efficient energy production, melatonin supports mitochondrial health and function.

4. Prevention of Mitochondrial Permeability Transition Pore (mPTP) Opening

The mitochondrial permeability transition pore (mPTP) is a channel that can open under conditions of mitochondrial stress, leading to the loss of membrane potential, ATP depletion, and eventual cell death via necrosis or apoptosis.

Melatonin has been shown to:

- **Inhibit mPTP opening:** By preventing the pathological opening of the mPTP, melatonin helps preserve mitochondrial membrane integrity and function, preventing the cascade of events that lead

to apoptosis or necrosis.

- **Preserve mitochondrial membrane potential ($\Delta\Psi_m$):** Melatonin stabilizes mitochondrial membranes, which is critical for maintaining the proton gradient required for ATP production.

5. Enhancement of Mitochondrial Biogenesis

Mitochondrial biogenesis, the process of producing new mitochondria, is essential for maintaining mitochondrial function, especially in aging tissues or those under metabolic stress. This process is regulated by the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), a key transcriptional coactivator involved in mitochondrial health.

Melatonin may enhance mitochondrial biogenesis by:

- Upregulating PGC-1 α expression, which leads to increased expression of nuclear and mitochondrial genes involved in mitochondrial replication and function.
- Supporting the production of new, functional mitochondria, which is crucial for tissues with high energy demands such as muscles and the brain.

6. Reduction of Mitochondrial Apoptosis

Mitochondria play a key role in the intrinsic pathway of apoptosis, releasing cytochrome c and other pro-apoptotic factors that trigger cell death. Excessive apoptosis, particularly in neurons, cardiac cells, or other vital tissues, can lead to degenerative diseases.

Melatonin helps reduce mitochondrial-mediated apoptosis by:

- Inhibiting cytochrome c release from the mitochondria, thus preventing the activation of the caspase cascade that leads to cell death.
- Upregulating anti-apoptotic proteins such as Bcl-2 and downregulating pro-apoptotic proteins like Bax, thus shifting the balance in favor of cell survival.

7. Regulation of Mitochondrial Dynamics

Mitochondrial dynamics involve processes such as mitochondrial fission (division) and mitochondrial fusion (joining of mitochondria). Proper regulation of these dynamics is critical for mitochondrial quality control and the removal of damaged mitochondria via mitophagy.

Melatonin has been found to:

- Support mitochondrial fusion by promoting a healthy mitochondrial network, which is important for the exchange of mitochondrial contents and maintaining mitochondrial function.
- Facilitate mitophagy, the selective removal of damaged mitochondria. By promoting mitophagy, melatonin ensures that dysfunctional mitochondria are removed, preventing them from accumulating and contributing to cellular dysfunction.

8. Modulation of Mitochondrial Uncoupling Proteins (UCPs)

Mitochondrial uncoupling proteins (UCPs) are involved in dissipating the proton gradient across the mitochondrial membrane, which can reduce ROS production at the cost of less ATP production.

Melatonin may regulate UCPs to:

- Prevent excessive uncoupling, ensuring that ATP production remains efficient.
- Minimize ROS production under conditions of oxidative stress by allowing some degree of uncoupling, which reduces electron leakage.

High-dose melatonin (400 mg per day) over a 12-week period can significantly enhance mitochondrial function by reducing oxidative stress, improving electron transport chain efficiency, preventing mitochondrial apoptosis, and promoting mitochondrial biogenesis. By preserving mitochondrial health and function, melatonin could help mitigate the progression of chronic diseases such as cardiovascular disease, neurodegenerative disorders, and metabolic syndromes. Furthermore, melatonin's broad range of actions

on mitochondrial dynamics and protection makes it a promising therapeutic agent for diseases where mitochondrial dysfunction plays a key role.

Potential Synergistic Benefits of Combining Melatonin and Lycopene

1. Enhanced Antioxidant Protection

- **Melatonin:** Melatonin is a direct free radical scavenger that easily crosses biological barriers, such as the blood-brain barrier and cellular membranes, allowing it to protect cells from oxidative stress in various tissues, including the brain, liver, and cardiovascular system. It also stimulates antioxidant enzyme activity, such as superoxide dismutase (SOD) and glutathione peroxidase, increasing the body's endogenous defense against oxidative damage.
- **Lycopene:** Lycopene, being a lipid-soluble antioxidant, primarily integrates into cell membranes and lipoproteins, where it protects lipids from oxidative damage. Lycopene is particularly effective at quenching singlet oxygen, one of the most reactive oxygen species.

Combined Effect: When used together, melatonin and lycopene can target different sites of oxidative stress. Melatonin acts both in lipid and aqueous environments due to its amphiphilic nature, while lycopene acts specifically in lipid-rich areas, such as cell membranes and lipoproteins. This complementary action could provide broader protection against oxidative damage, which is particularly beneficial in conditions like cardiovascular disease and cancer, where oxidative damage is a key contributor.

2. Reduction of Inflammation

Melatonin: Melatonin inhibits the NF- κ B pathway, a key regulator of inflammation, thereby reducing the production of pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6. Melatonin also reduces the activation of inflammasomes, which are involved in chronic inflammation.

Lycopene: Lycopene also exerts anti-inflammatory effects by inhibiting the NF- κ B pathway and reducing the

levels of pro-inflammatory cytokines. Lycopene additionally downregulates other inflammatory mediators like IL-8 and MCP-1 (monocyte chemoattractant protein-1), which are involved in immune cell recruitment and atherosclerosis.

Combined Effect: By inhibiting multiple pro-inflammatory pathways, combining melatonin and lycopene could result in a stronger anti-inflammatory effect. This could be especially useful in diseases where inflammation plays a central role, such as in atherosclerosis, arthritis, and inflammatory bowel disease (IBD). The combination might help reduce chronic inflammation more effectively than either compound alone.

3. Improved Lipid Metabolism

Melatonin: Melatonin has been shown to improve lipid metabolism by reducing levels of low-density lipoprotein (LDL) and increasing levels of high-density lipoprotein (HDL) cholesterol. This effect helps reduce the risk of atherosclerosis in individuals with dyslipidemia, including those resistant to statin therapy.

Lycopene: Lycopene similarly improves lipid profiles by reducing LDL oxidation, which is a key step in the development of atherosclerosis. Lycopene also has cholesterol-lowering effects and has been associated with a reduced risk of cardiovascular disease.

Combined Effect: The combination of melatonin and lycopene may provide a more comprehensive approach to managing dyslipidemia. While melatonin influences cholesterol metabolism and HDL levels, lycopene specifically protects LDL from oxidative damage, which is critical in preventing plaque formation in arteries. Together, they could provide stronger protection against cardiovascular diseases than either agent alone.

4. Potential Neuroprotection

Melatonin: Melatonin is widely studied for its neuroprotective effects, particularly in conditions like Alzheimer's disease and Parkinson's disease. It helps reduce oxidative stress in neurons, modulates mitochondrial function, and reduces inflammation in the brain. Melatonin also regulates circadian rhythms, which can help improve sleep, a factor that is often disrupted in neurodegenerative diseases.

es.

Lycopene: Lycopene has also been shown to protect neurons from oxidative damage and reduce neuroinflammation. Studies suggest that lycopene may protect against cognitive decline by reducing the buildup of amyloid plaques and neurofibrillary tangles in Alzheimer's disease.

Combined Effect: Together, melatonin and lycopene could offer enhanced neuroprotection by reducing oxidative stress, neuroinflammation, and mitochondrial dysfunction in the brain. This combination could be particularly beneficial for preventing or slowing the progression of neurodegenerative diseases, as well as improving cognitive function in aging populations.

5. Potential Anti-Cancer Effects

Melatonin: Melatonin has been studied for its anti-cancer properties, particularly in breast cancer, prostate cancer, and colorectal cancer. It modulates cell cycle regulation, enhances the efficacy of chemotherapy, and reduces the growth of cancer cells by inducing apoptosis (programmed cell death) and inhibiting angiogenesis (formation of new blood vessels that feed tumors).

Lycopene: Lycopene is also associated with anti-cancer effects, particularly in reducing the risk of prostate cancer. Lycopene inhibits cell proliferation, induces apoptosis, and reduces oxidative DNA damage, which can lead to mutations and tumor development.

Combined Effect: The combination of melatonin and lycopene could enhance anti-cancer effects through multiple pathways. While melatonin works through circadian regulation and immune modulation, lycopene specifically targets oxidative DNA damage and cell proliferation. This dual action could potentially provide a stronger defense against the development and progression of cancer, particularly in hormone-responsive cancers like prostate and breast cancer.

Safety and Potential Interactions

Safety Profile: Both melatonin and lycopene are considered safe when used as supplements at recommended

doses. Melatonin is commonly used for sleep regulation and has a good safety profile, even with long-term use. Lycopene is widely consumed through the diet, particularly in tomato-based foods, and is also safe in supplement form. There are no known major adverse interactions between the two compounds.

Potential Interactions: While no significant negative interactions have been reported between melatonin and lycopene, both substances modulate oxidative stress and inflammation. Monitoring dosage might be necessary to avoid excessive antioxidant activity, although this is more theoretical than a practical concern.

Combining melatonin and lycopene holds great promise for managing various health conditions due to their complementary antioxidant, anti-inflammatory, and lipid-modulating properties. The combination could be particularly useful in managing diseases characterized by oxidative stress and chronic inflammation, such as cardiovascular diseases, neurodegenerative disorders, and certain cancers. Further research, including clinical trials, is warranted to explore the full potential of this combination and optimize dosing strategies for maximum therapeutic benefit.

Limitations and Future Directions

While the findings of this study are promising, there are several limitations that should be considered. The relatively small sample size may limit the generalizability of the results, and the short duration of the study may not capture the long-term effects of melatonin supplementation. Additionally, the study did not explore the potential synergistic effects of combining melatonin with other antioxidant therapies, such as lycopene, which may offer enhanced therapeutic benefits. Further research is warranted to explore the long-term efficacy of melatonin in larger, more diverse populations and to investigate its potential use in combination with other antioxidant therapies.

In conclusion, melatonin rectal suppositories represent a novel therapeutic approach for managing oxidative stress, dyslipidemia, and inflammation in statin-resistant patients. The significant improvements in oxidative stress markers, lipid profiles, and clinical outcomes observed in this study highlight the potential of melatonin as a valuable

therapeutic agent in this patient population. The anti-inflammatory and antioxidant properties of melatonin, combined with its ability to improve lipid metabolism, make it a promising candidate for managing chronic diseases associated with oxidative stress. Future studies should aim to further investigate the long-term benefits of melatonin and explore its potential synergistic effects with other antioxidant therapies.

Conclusion

The findings of this study demonstrate that melatonin rectal suppositories provide a novel and effective therapeutic option for managing oxidative stress, dyslipidemia, and inflammation in statin-resistant patients. Statin resistance, characterized by the inability to achieve optimal lipid levels despite high-dose statin therapy, presents a significant challenge in managing cardiovascular risk. This study provides compelling evidence that melatonin offers a promising alternative for improving lipid metabolism, reducing oxidative stress, and mitigating systemic inflammation in this patient population.

The most notable outcomes of this study include the significant reductions in oxidative stress markers such as malondialdehyde (MDA), a widely recognized indicator of lipid peroxidation and oxidative damage. Melatonin's ability to lower MDA levels suggests that it effectively mitigates oxidative damage to cellular membranes, which is crucial for reducing the risk of chronic conditions such as atherosclerosis, cancer, and neurodegenerative diseases. Furthermore, the increase in total antioxidant capacity (TAC) in the melatonin group underscores melatonin's potent antioxidant activity, enhancing the body's overall defense system against reactive oxygen species (ROS).

Melatonin's anti-inflammatory effects were also evident in this study, as indicated by significant reductions in C-reactive protein (CRP) and interleukin-6 (IL-6) levels. Chronic inflammation is closely associated with the progression of numerous diseases, including cardiovascular disease, rheumatoid arthritis, and cancer. The reductions in CRP and IL-6 levels highlight melatonin's role in attenuating systemic inflammation, offering further therapeutic benefits for individuals with chronic inflammatory conditions. By in-

hibiting the NF- κ B pathway, melatonin modulates the production of pro-inflammatory cytokines, helping to prevent the chronic inflammation that contributes to disease progression.

The improvements in lipid profiles observed in the melatonin group further emphasize the therapeutic potential of melatonin for statin-resistant patients. The significant reductions in low-density lipoprotein (LDL) cholesterol, combined with the increase in high-density lipoprotein (HDL) cholesterol, suggest that melatonin can effectively regulate lipid metabolism and reduce cardiovascular risk. LDL cholesterol is a major contributor to atherosclerosis and cardiovascular disease, and its reduction is crucial for preventing cardiovascular events. The increase in HDL cholesterol, often referred to as "good" cholesterol due to its role in removing excess cholesterol from arterial walls, provides additional cardiovascular benefits by promoting healthy lipid metabolism.

Lycopene, another antioxidant explored in this study, also demonstrated improvements in oxidative stress markers, lipid profiles, and inflammatory biomarkers. Lycopene's ability to reduce MDA levels, increase TAC, and lower CRP and IL-6 levels suggests that it exerts similar protective effects as melatonin. However, the slightly greater improvements in the melatonin group indicate that melatonin may have broader therapeutic effects, potentially due to its additional roles in regulating circadian rhythms and mitochondrial function. Nevertheless, lycopene remains a valuable antioxidant with significant health benefits, particularly in its ability to protect against lipid peroxidation and oxidative damage.

The combination of melatonin and lycopene holds potential for synergistic effects, offering enhanced protection against oxidative stress, inflammation, and lipid abnormalities. Both agents act through different but complementary mechanisms, with melatonin primarily working through free radical scavenging and circadian regulation, while lycopene protects lipids from oxidation and modulates inflammatory pathways. This combination may provide even greater therapeutic benefits, particularly in conditions where oxidative stress and inflammation are prominent, such as cardiovascular disease, cancer, and neurode-

generative disorders. Future studies should investigate the potential benefits of combining melatonin and lycopene in clinical settings, with a focus on optimizing dosing strategies and exploring long-term outcomes.

While this study provides strong evidence for the efficacy of melatonin rectal suppositories, there are several limitations that warrant further investigation. The relatively short duration of the study and the small sample size may limit the generalizability of the findings. Long-term studies are needed to explore the sustained effects of melatonin supplementation and to assess its safety and efficacy over extended periods. Additionally, further research is needed to explore the potential synergistic effects of combining melatonin with other antioxidant therapies, such as lycopene, and to investigate its role in managing other chronic conditions associated with oxidative stress and inflammation.

In conclusion, the administration of melatonin rectal suppositories offers a novel, effective, and well-tolerated approach to managing oxidative stress, regulating lipid metabolism, and reducing inflammation in statin-resistant patients. These findings underscore the therapeutic potential of melatonin in improving clinical outcomes and reducing cardiovascular risk in a population that struggles with traditional lipid-lowering therapies. Future research should focus on exploring the long-term benefits of melatonin and its potential combination with other antioxidants to optimize treatment strategies for patients with chronic oxidative stress-related diseases.

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Informed Consent Statement

Yes

Data Availability statement

The authors confirm that the data supporting the

findings of this study are available within the article and its supplementary materials.

Author Contributions

All authors contributed to manuscript revision and have read and approved the submitted version.

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