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Original Article

Evaluation of Anti-atherosclerotic Effects of Melatonin Interference with Inflammatory and Oxidative Stress Pathway in Male Rabbits

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ABSTRACT

Atherosclerosis is the primary cause of death worldwide. It is now commonly acknowledged that it is a persistent inflammatory process. Minor inflammation, increased oxidative stress, and lipid peroxidation all play the essential roles in the atherosclerosis progression. Melatonin (N-acetyl-5-methoxytryptamine) is a neuroendocrine hormone discovered in the bovine pineal gland. The antioxidant action of melatonin is manifested to its direct effects via M1,2 receptors. It not only increases antioxidant enzymes, but also suppresses mesenchymal cell apoptosis. Melatonin is anti-inflammatory and anti-oxidant. In contrast to well-known Instead of following an enzymatic pathway of reduction after oxidation, as do endogenous antioxidants such carotene and vitamins E and C, melatonin binds permanently to free radicals, which the kidneys eliminate. In comparison to the induced untreated group, melatonin has a significant impact on lipid parameters (P>0.001). Melatonin significantly reduced the elevation in ICAM and a mild effect on the aorta thickness compared with induced untreated groups (P<0.05). The drug restores aortic GSH and SOD level (P<0.001). The aim of this research is to evaluate whether melatonin can protect rabbits against atherosclerosis and their role in inflammatory and oxidative pathway. Twenty-four domestic male rabbits from the surrounding area were divided into three groups: Group One, normal Control group (n = 8). Group Two (n = 8): Rabbits were fed a 1% cholesterol diet (induced untreated group). Group Three (n = 8): 1% cholesterol diet + oral melatonin 10 mg/kg once per day before breakfast. Animals fed with an atherogenic diet had lower levels of GSH, SOD, and higher levels of total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density cholesterol, very low-density cholesterol, a therogenic index, iCAM, and intimal thickness of the aorta, as compared with controls (P<0.001). In comparison with the induced untreated group, melatonin has a significant impact on lipid parameters (P>0.001). Melatonin significantly reduced the ICAM elevation and a mild effect on aorta thickness compared with induced untreated groups (p<0.05). The drug restore aortic GSH and SOD level (P<0.001). The findings of the current study suggest that melatonin reduce the evolution of atherosclerosis in by meddling with inflammatory and oxidative processes and affecting lipid parameters, it was possible to treat hypercholesterolemic rabbits.

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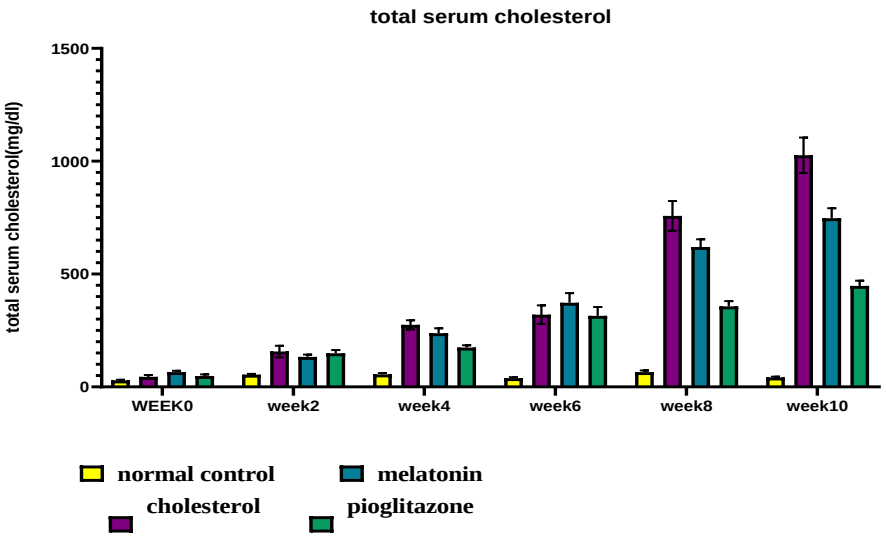
GRAPHICAL ABSTRACT



Introduction

Atherosclerosis is regarded as a persistent inflammatory reaction of the wall of arteries irresponsive to dyslipidemia combined with endothelial disturbance involving the local vascular cells are activated together with the inflammatory leukocyte recruitment [1].

The persistent arterial vascular wall irritation is considered to produce multifocal plaque formation. Plaque is a sticky substance comprised of fat, cholesterol, calcium, and other things [2]. As plaque builds up, the arteries become rigid, narrow acute, and chronic lumina blockage, irregular blood flow, and reduced oxygen availability to target organs are all possible outcomes [3].

Many inflammatory mediators have been identified with an impact on the progression of atherosclerotic plaques. CD40L produced within the plaque, for example, has been found to boost tissue factor expression in atherosclerotic plaque. Several inflammatory mediators are produced by smooth cells within the atherosclerotic plaque, including interleukin (IL)-1ß, tumor necrosis factor (TNF), IL-6, M-CSF, MCP-1, IL-18, IL-17A, and CD-40L [4, 5].

A cute-phase reactants such as (CRP), (TNF), (IL-6), serum amyloid A, and fibrinogen are among the most significant inflammatory markers because they give a measure of the inflammatory process in the arterial wall that is indirectly cytokine-dependent [5].

The C - reactive protein may play a direct role in the etiology of atherosclerosis, according to research. CRP is highly up-regulated in atheromatuos plaques, where it may increase LDL uptake by macrophages, a critical stage in atherogenesis, according to which the endothelial cells may also express intercellular adhesion molecules, which could make it easier for circulating monocytes to find plaque locations. In addition, C-reactive protein can bind and activate complement in serum, which may result in an increase in inflammation. These effects appear to be mediated via endothelin-1 and IL-6 release produced by CRP [6].

Antioxidants are any chemical (molecule, compound, or enzyme) that has a substantial antioxidant effect. The majority of antioxidants are electron donors, which combine with free radicals to produce harmless end products like water. As a result, antioxidants protect cells from oxidative stress and damage. Antioxidants come in various forms [7].

TNF interferes with GSH production through different pathways, resulting in reduced GSH levels. TNF-alpha production is also increased by oxidative stress.As a result of the GSH disruptions and increased TNF-alpha production/activation, a pathogenic "loop" or vicious cycle develops [8, 9].

Melatonin, a term that refers to a melanophore-contracting hormone, was initially found as a skin-lightening chemical that acts on frog and fish

melanocytes. Melatonin was later discovered to be present in all vertebrates, released rhythmically by the pineal gland, and implicated in the circadian regulation and occasionally seasonal rhythms [10].

A hormone produced by the pineal gland called melatonin helps regulate physiological functions like sleep, circadian rhythm, and neuroendocrine functions. Numerous plants contain melatonin, which has anti-inflammatory, antioxidant, hepatoprotective, cardioprotective, and neuroprotective properties [11].

Sites fall into two categories: M L1 (high affinity [picomolar]) and M L2 (low affinity [nanomolar]). Adenylate cyclase activity in target cells is inhibited by the activation of ML1 melatonin receptors, which belong to the family of guano sine triphosphate-binding proteins (G protein-coupled receptors). These receptors certainly play a role in the control of reproductive, circadian, and retinal function. Although phosphoinositide hydrolysis stimulation is connected to the ML2 receptors, their location is unknown. Two distinct forms of a high-affinity melatonin receptors, designated Mel1a and Mel1b, were cloned from many mammals, including human by using the polymerase chain reaction (PCR) [12].

Neural receptors are likely to control circadian rhythms (e.g., those found in the hypothalamic suprachiasmatic nucleus). Non-neural melatonin receptors, such as those found in the pars tuberalis of the pituitary; almost certainly control reproductive function, especially in species that breed seasonally. In contrast, receptors found in peripheral tissues, such as arteries, may control cardiovascular function and body temperature [13, 14]. The aim of this research is to evaluate whether melatonin can protect rabbits against atherosclerosis and their role in inflammatory and oxidative pathway.

Materials and Methods

Twenty-four local domestic male rabbits from the surrounding area were divided into three groups as follow:

Group I, normal control group (n = 8), Group II (n = 8): Rabbits fed a 1% cholesterol diet (induced untreated group), and Group III (n = 8): 1% cholesterol diet + oral melatonin 10 mg/kg once a day before breakfast.

The blood samples were taken to measure blood triglycerides (TG), total cholesterol (TC), HDL-C, VLDL-C, and ICAM before and after each of the atherogenic meals that were consumed over two weeks. After 10 weeks, the aorta was removed to measure the intimal thickness, reduced glutathione (GSH), and aortic SOD. The usual diet for rabbits contained 10% wheat, 40% grass powder, 13% soybean cake, 20% maize, 10% wheat bran, 3% fish flour, 1% salt, 3% bone meal, and 1% multivitamins (percent by weight). 32 domestic male rabbits from the local area were used in this study. They were weighed about 1.1-2 kg. They were housed in the animal house at the Al-Kufa Pharmacy for 12 hours at 25 °C ambient 60-65%. They were provided with the unlimited access to tap water and a standard chow diet. Throughout the first week of adaptation in tiny removed from the protocol to reduce any potential effects on hypercholesterolemic atherosclerosis.

Results and Discussion

Both groups that received melatonin and the induced untreated group experienced a slight but significant increase in body weight. The body weights of the melatonin-receiving group and the control group had significantly changed by the time the sacrifice (10 weeks) was made. The body weight of the melatonin-receiving group and the untreated group increased barely. The serum levels of TC, TG, LDL, and VLDL-C were significantly different between the normal control group (I) and the groups on an atherogenic diet (II and III), and there were significant differences in the serum level of induced untreated group (II) and melatonin treated group (III) (Figure 1). The baseline values of serum ICAM were not statistically significant in any of the groups prior to the trial. The ICAM levels in the induced untreated group significantly raised after 2 weeks of atherogenic diet (Figure 2). After 8 weeks, the ICAM level significantly increased compared with zero time. After 10 weeks, the serum ICAM levels of the

melatonin treated groups were considerably (P<0.001) lower than those of the induced untreated group (II). The treated groups had significantly greater aortic GSH levels than the induced untreated group (II). Melatonin (III) treated group had significantly higher aortic SOD levels after 10 weeks than the induced untreated group (II). There was an insignificant improvement (P>0.05) in atherosclerosis histological intima thickness (Tabels 1, 2 and 3, Figures 3, 4 and 5).

Table 1: Variations in three experimental groups' serum lipid profiles (TC, TG, and HDL) in rabbits by using a paired T-test, the data were presented as Mean± SEM (N=8 in each group)

		T C (mg/dl)	T G (mg/dl)	HDL (mg/dl)
Control Normal (I)	Zero time	28.37±3.28	88.7±2.04	20.20±0.72
	10 weeks	44.63±3.93	75.41±8.44	17.05±3.23
Induced untreated (II)	Zero time	44.64±8.25	78.36±6.89	24.8±4.61
	10 weeks	1026.38±14.83[a]	451.7±14.3[a]	33.3±5.23[a]
Melatonin group (III) 10 mg/kg	Zero time	65.37±5.87	74.20±3.01	12.5±4.60
	10 weeks	747.37±12.90[a]	399.4±13.43[a]	41.71±6.74[a]

[a]P < 0.001

Table 2: Variations in three experimental groups' serum levels of the inflammatory marker ICAM-1 in rabbits by using a paired T-test, the data were presented as Mean± SEM (N=8 in each group)

		ICAM-1 (pg/ml)
Control normal (I)	Zero time	55.4±2.34
	10 weeks	70.50±3.84
Induced untreated (II)	Zero time	73.2±3.21
	10weeks	125.8±1.67[a]
Melatonin group (III)10mg/kg	Zero time	65.2±1.43
	10weeks	100.1±6.55[a]

[a]P < 0.001

Table 3: The average values of the SOD and GTH parameters for aortic oxidative stress in rabbits across three experimental groups by using a paired T-test, the data were presented as Mean ±SEM (N=8 in each group)

	Aortic GSH (ng/l)	Aortic SOD (pg/ml) aorta
Control normal (I)	23.36 ± 1.76	330.4±27.20
Induced untreated (II)	15.23 ± 1.43[a]	180.1±23.92[a]
Melatonin group (III)	21.69 ± 1.09[b]	294.2±18.83[b]

[a]P<0.05 as compared with induced untreated

[b]P < 0.05 as compared with normal control

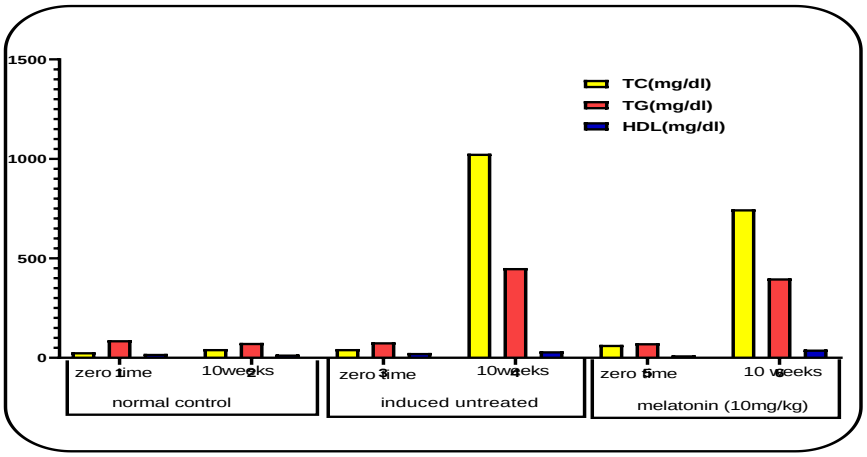


Figure 1: The impact of melatonin 10 mg/kg/day treatment on the levels of serum TC, TG, and HDL during the experimental treatment

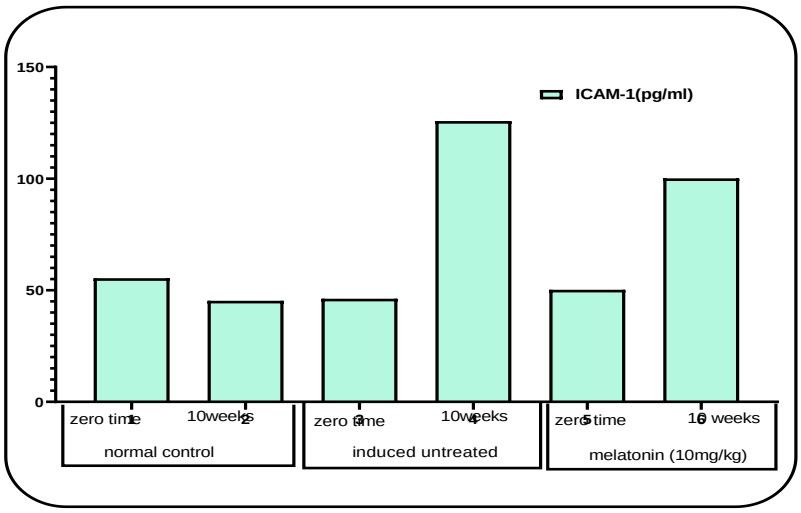


Figure 2: Comparison between two control groups and the impact of melatonin 10 mg/kg/day treatment on serum ICAM-1 (pg/ml) levels (normal and induced untreated)

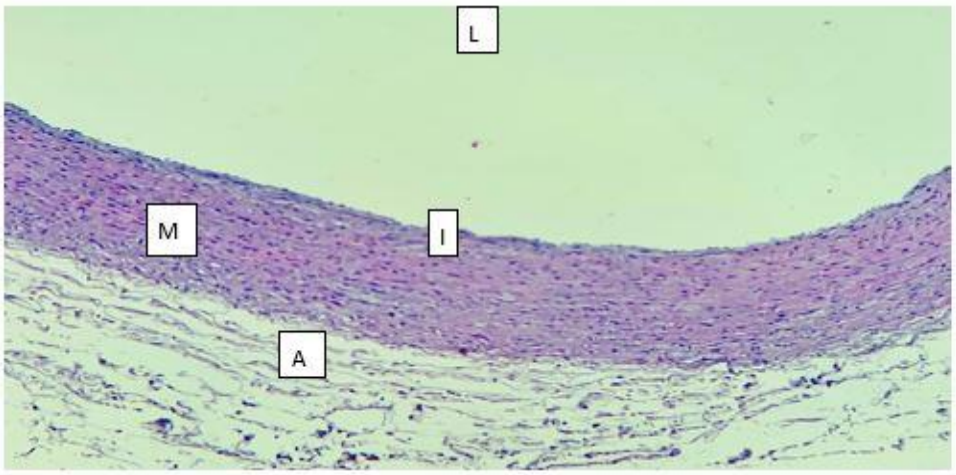


Figure 3: The formation of arterial wall layers in the aortic arch of rabbits fed a normal diet for 10 weeks (the control group); lumen (L), intima (I), regularly spaced smooth muscle fibers, medium (M), and adventitia are all present and intact continuous endothelium (A). Haematoxylin and eosin staining of the slice (number 10)

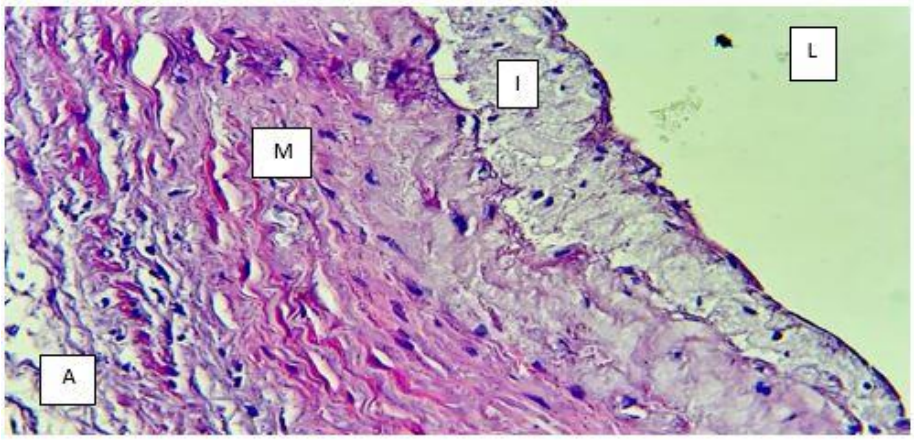


Figure 4: Photo micrograph of a histo-morphometric section in the aortic arch of rabbits fed an atherogenic diet for 10 weeks (induced and untreated) reveals diffuse intima thickening and the convergence of lipid collections, which results in an extracellular dense accumulation of fat in a precisely defined area; (I) intima, (M) media, (A) adventitia, and (L) lumen. Haematoxylin and eosin staining of the slice (number 10)

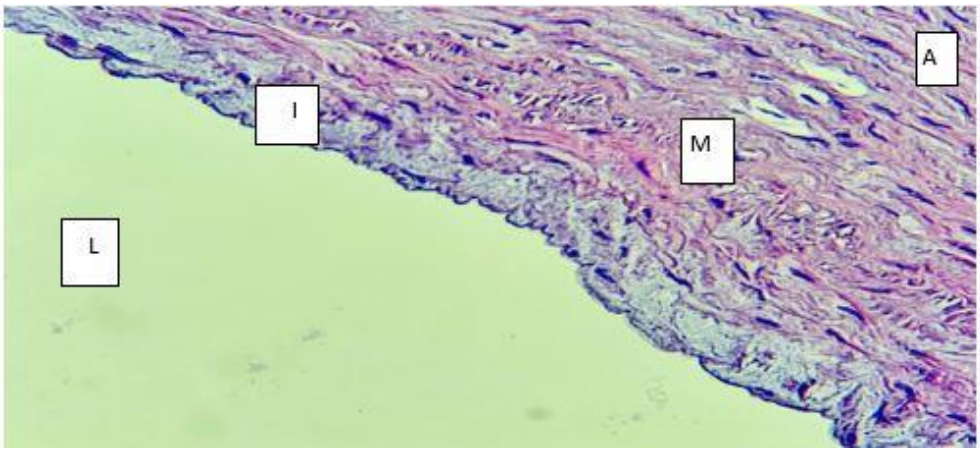


Figure 5: Photo micrograph of histo-morphometric section in aortic arch of rabbits on melatonin hyperlipidemia for 10 weeks show an insignificant decrease in the aortic intima thickness, as compared with induced untreated; (I) intima, (M) media, (A) adventitia, and (L) lumen. The section stained with haematoxylin and eosin (×10)

A common and serious complication of type two diabetes is accelerated atherosclerosis, which is accompanied by a high risk of premature mortality from cardiovascular disease (such as coronary heart disease) [13]. Therefore, it is essential for the management of individuals with this entity to avoid the onset, or development of atherosclerosis, and maintain the appropriate glycemic control. The goal of the current study was to evaluate how pioglitazone affected the oxidative and inflammatory pathways to treat atherosclerosis. Our findings showed that eating a diet high in cholesterol for 10 weeks increased all serum cholesterol profile part and accelerated the development of atherosclerotic lesions, such as thickening of the intima and/or accumulation of lipid droplets beneath endothelial cells in the carotid artery. Furthermore, the findings of the current study demonstrated that pioglitazone treatment could dramatically reduce ICAM-1 and other inflammatory markers, which were shown to be much greater in atherosclerotic rabbits. This particular study shows that treatment with pioglitazone appeared to have a significant effect on lipid parameters when compared with the induced untreated group.

Melatonin had minor but substantial effects on the lipid profile in the current investigation, as compared to the induced untreated group. This conclusion may be connected to the possibility that the impact of a high-cholesterol meal could conceal any modification to lipid measurements.

The result of our study is different from that reported by Ismail and Mahmood (2022) who found that there was a highly significant difference and variability bout changes in lipid profiles in melatonin group than without melatonin group and this difference may be due to that this study was shorter than our study, and further they used streptozotocin-induced rat while we used atherosclerosis induced rabbits [14].

Furthermore, it has recently been discovered that while melatonin has no effect on total cholesterol, it greatly increases the serum triglyceride and HDL-C level [15, 16].

In comparison to the induced untreated group, melatonin dramatically decreased the rise of proinflammatory ICAM markers in rabbits. Suggesting that melatonin has a protective effect on atherosclerosis induced by high cholesterol and suppressing mRNA expression also reduces the generations of pro-inflammatory cytokines [14].

Moreover, melatonin may protect against atherosclerosis by boosting anti-atherosclerotic and anti-inflammatory vaspin and lowering the production of pro-inflammatory visfatin and STAT-3. Likewise, recent studies revealed the anti-inflammatory effect of melatonin on ICAM as a marker. Leukocyte recruitment that follows inflammation of the vascular endothelium is the initial step in the atherosclerosis development [17, 18].

Melatonin significantly reduced the rise in serum SOD generated by high cholesterol feeding in the current investigation, indicating the ROS reduction and concomitant lipid peroxidation. In addition, melatonin markedly raised GSH levels, preventing the GSH depletion in rabbits with high cholesterol and maintaining the antioxidant reserve necessary for vascular defense against lipid peroxide.

This is in agreement with Li *et al.* (2022). They discovered that the anti-oxidative effects of melatonin in heart failure were mostly independent of its ejection fraction and that its use reduced lipid peroxidation and controlled the activities of both enzymatic and non-enzymatic antioxidant mechanisms [19, 20].

In addition, melatonin has a positive impact on the oxidative stress parameters, leading to a notable increase in serum SOD activity and total serum antioxidant capacity and may control the atherogenic index to influence cholesterol metabolism and control antioxidant activity with GSH and SOD [21-30]. Antioxidants are any chemical (molecule, compound, or enzyme) that has a substantial antioxidant effect. The majority of antioxidants are electron donors, which combine with free radicals to produce harmless end products like water. Therefore, antioxidants protect cells from the oxidative stress and damage. Antioxidants come in various forms [7].

TNF interferes with GSH production through different pathways, resulting in reduced GSH levels. TNF-alpha production is also increased by oxidative stress. As a result of the GSH disruptions and increased TNF-alpha production/activation, a pathogenic "loop" or vicious cycle develops [8, 9].

Conclusion

The findings of the current study suggest that melatonin may reduce the atherosclerosis evolution in hypercholesterolemic rabbits by interfering with inflammatory and oxidative pathways and influencing lipid parameters.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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