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Exploring the Role of Melatonin in Meditation on Cardiovascular Health

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Abstract: Cardiovascular diseases are the leading cause of disease burden globally. Sleep and cardiovascular connection represent a two-way lane. Recently, many reports have suggested that meditation practices have a beneficial effect on cardiovascular diseases. But the exact mechanism was not known. Several reports suggest that meditation induces the secretion of melatonin. The rhythm of melatonin follows a sleep pattern. Thus, the present hypothesis correlates the plausible mechanisms involved in meditation with enhancing cardiac health through melatonin synthesis. An altered modern lifestyle decreases the level of melatonin which disrupts the circadian rhythm, and subsequently, there is a high incidence of cardiovascular diseases. The disrupted cardiac energy metabolism is distorted due to altered circadian rhythm with elevated ROS. The increased level of ROS activates the inflammatory mediators' cytokines and damages the DNA, resulting in altered cardiac physiology. Melatonin regulates the circadian rhythm and acts as a silent regulator for the cardiac energy balance. Melatonin is the central player of circadian rhythm, and it protects cardiomyocytes by acting as an antioxidant, anti-inflammatory mediator, and repairing DNA damage. Meditation induces melatonin and improves cardiac health through the aforementioned mechanisms.

Keywords: cardiovascular diseases; meditation; melatonin; ROS; DNA repair; circadian rhythm; Glucose; lipid metabolism.

1. Introduction

1.1. Cardiovascular disease and meditation.

Cardiovascular diseases (CVD) remain one of the most common causes of mortality globally among non-communicable diseases [1–3]. Compared to the high-income countries, CVD mortality in low- and middle-income countries is extremely high due to limited access to effective preventive and management programs [4–9]. In these settings, inexpensive intervention and lifestyle changes can prevent CVD development and improve outcomes.

From the wake of this century, yoga and meditation have attracted more and more attention as effective interventions to improve health. Meditation has beneficial effects on various organs, including the heart [10]. A practice of 12-week mindfulness meditation training for heart patients under usual care displayed significant improvement in blood pressure, heart rate, respiratory rate, NT-pro BNP level, and the results of 6 minutes walk test [11,12]. Meditation practices improve the rehabilitation process in patients with cardiovascular diseases [13,14]. American Heart Association advocates meditation as an adjunct therapy to enhance cardiac health [15]. The present article aims at comprehending the possible mechanisms through which meditation protects cardiac functions.

1.2. Meditation and melatonin.

Meditation is defined as a condition of contemplation, concentration, and reflection [16–18]. The practice has a thousand-year history of improving spiritual and emotional well-being by achieving physical relaxation, inner calmness, and psychological balance by the participator, examining their thoughts and feelings. Mantra meditation, concentrating on a particular subject/point (such as heartfulness meditation, *kundalini* meditation), and mindfulness meditation are just examples of meditation types being practiced nowadays [19–21]. The main goal of meditation is to create awareness of a given moment and forget the past bad moments in a non-judgmental fashion [22,23]. Yoga is a set of techniques, including postures, breath control, and meditation originated in India. Tai chi and qigong, traditional Chinese martial arts and medicine, also include meditation practices [24,25].

In the past two decades, a growing number of research reports suggested that meditation practices cure stress, pain, and anxiety-related conditions through psychological intervention [26–29]. Meditation is helpful as an antidote to both physiological and mental stress. Psychological stress is experienced as encountering obstacles to fulfilling an individual's requirements and aspirations and a perceived threat. The body responds to stress with increased heart rate, blood pressure, breath rate, sweating, weakened immunity, and blood clotting. In a meditative state, the human body switches into a state of restful awareness. The body responds with decreased heart rate, normalization of blood pressure, quiet breathing, reduced stress hormone production, strengthened immune system, reduced sweating, and improved blood flow. These observations suggest that meditation has a dramatic long-term structural effect on the body [30–33]. Recent findings demonstrate that meditation increases melatonin levels [10,34–36]. Meditation raises melatonin levels by delaying the hormone's hepatic metabolism or increasing its production in the pineal gland [37]. Melatonin receptors have been found all through the cardiovascular system, including in various vascular tissues [38,39]. Platelet aggregation, nocturnal hypertension, and serum catecholamine levels have all been found to be reduced by exogenous melatonin [40]. Thus, the influence of melatonin on cardiovascular risk factors via meditation is discussed in this review, as well as current advances in our understanding of meditation and melatonin's effects on cardiovascular illnesses.

2. Melatonin and Circadian Rhythm

Meditation practices synchronize the hypothalamo-pituitary-adrenal (HPA) axis and normalize the levels of cortisol and catecholamine [41,42]. Moreover, meditation increase the level of dehydrosterone [43] and anterior hypophyseal hormones such as growth hormone, thyrotropin-releasing hormone (TRH), prolactin, and melatonin [44].

Melatonin has a crucial function in the physiological control of sleep, both in blind and sighted individuals [45]. The rhythm of melatonin follows a sleep pattern [46]. Melatonin exerts hypnotic properties by inhibiting the suprachiasmatic nucleus [47] and promoting peripheral vasodilation to hypothermic reaction. Melatonin is typically used to treat sleep cycle disruptions attributable to jetlag and insomnia [48]. Melatonin is not just an antioxidant and immunomodulatory agent [49]; it also acts as oncostatin and improves well-being [45]. Aging decreases the release of melatonin and thus influences sleep quality in the elderly. It was shown that mediation practices increase melatonin, serotonin, and noradrenaline levels. Meditation practices increase melatonin by restricting its hepatic metabolism or increasing pineal gland synthesis. Considering the melatonin function in sleep management, mediation activities may improve sleep quality by increased release of melatonin [50].

Sleep has been correlated with lowered heart rate, blood pressure, breath rate and rhythm, oxygen intake, fear or excitations, and reduced basal metabolic level [50]. In cardiovascular conditions, decreased level of circulating melatonin has been observed. On the other hand, the increased melatonin level protects the heart from other cardiovascular diseases in several mechanisms [51]. Until now, the mechanism of melatonin-mediated protection of cardiac function has not been elucidated. This review focuses on deriving the underlying mechanism of melatonin's protective effect through meditation.

2.1. Role of circadian rhythm in cardiac metabolism correlated with melatonin.

The cardiovascular system exhibits circadian rhythmicity with their acrophases in different parts of the 24-hour cycle [52,53]. The regular synchronization of circadian rhythm signals a biological system's functioning in a coordinated manner [52,54]. The circadian clock's timing is regulated by a signal obtained from the suprachiasmatic nucleus (SCN) through the retina [55,56]. The circadian rhythm is regulated by the clock gene [57,58]. Any disturbance in the clock gene renders impairment in the cardiovascular system [59]. A change in blood pressure synchrony with the circadian rhythm was observed in hypertensive rat strains [59,60].

In humans, circadian rhythm regulates carbohydrate metabolism, essential for glucose homeostasis and energy balance. The disparity between glucose and insulin in tissues and blood cells causes various disorders, including metabolic syndrome, obesity, type 2 diabetes, and cardiovascular diseases [61]. Reaven reported that insulin resistance and elevated circulating postprandial TAG concentration cause cardiovascular diseases [62]. For example, the individuals working in shifts at late hours who consume their food late night have relative glucose and lipid intolerance [63]. Among the workers working night shifts, elevated levels of circulating TAG are observed irrespective of their energy and nutrient intake because of the disrupted circadian rhythm. The increased level of TAG promotes cardiovascular disease [64]. Comparatively, night-time workers have an elevated chance of having cardiovascular diseases than day-time workers [65].

Melatonin is secreted when the eyes do not receive light, and they accelerate the production of 7α-hydroxypregnenolone. Understandably, the regulation of 7α - hydroxypregnenolone synthesis is central to animal circadian rhythms [55,56]. Circadian change in spontaneous locomotor activity concerning the 7α-hydroxypregnenolone synthesis and melatonin secretion were evaluated [55,56]. A strong association between circadian rhythm and metabolism has been well established. [66–68]. The circadian rhythm regulates glucose homeostasis and energy balance through insulin [61].

Melatonin can influence the circadian rhythm in the cardiovascular system by following pathways such as i) central oscillator in the SCN; ii) the sympathetic output to the heart and vessels; iii) interactions with other hormonal systems involved in cardiovascular system regulation [57]. Thus, melatonin protects the cardiovascular system through its influence on circadian rhythm. Continuous practices of meditation may influence melatonin production. Overall, it is apparent that melatonin protects the heart by regulating circadian rhythm (Figure 1).

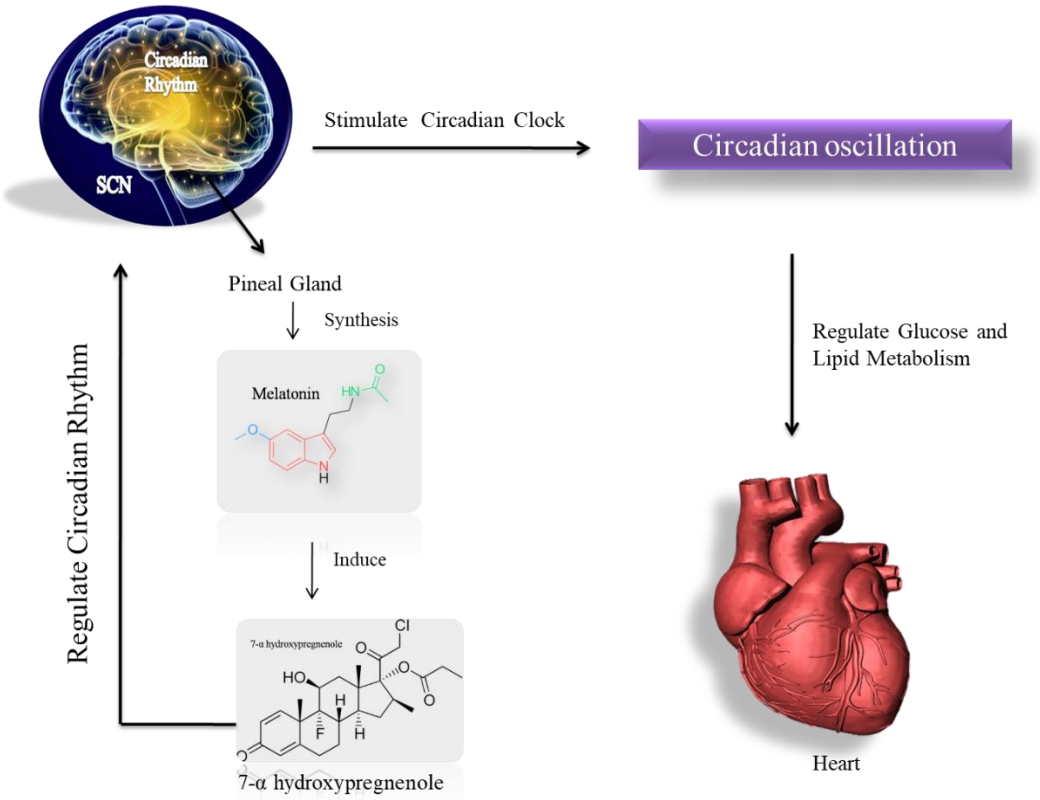

Figure 1. Role of melatonin in circadian rhythm. Regulation of circadian rhythm via melatonin synthesis correlated with glucose and lipid metabolism.

3. Role of Melatonin in Cardiac Energetic Metabolism

The energy needs demand of a healthy heart is primarily met by fatty acids (80%) and the rest from glucose (20%). At rest, cardiomyocytes use 15-20% of maximal oxidative capacity [69]. Any metabolic disturbance triggers cardiac dysfunction. Altered cardiac energy metabolism impairs ATP synthesis [70], gradually increasing cardiac failure risk [71]. On the other hand, dyslipidemia is a significant risk factor for cardiovascular diseases [72]. Melatonin decreases low-density lipoprotein (LDL) level and body weight in high-fat diet-induced non-alcoholic fatty liver disease mice [72].

Studies have reported that melatonin influences carbohydrate metabolism [73,74] in pinealectomized animals. It upregulates the expression levels of enzymes involved in lipolysis, β-oxidation, and mitochondrial biogenesis-related genes [74]. Thus, melatonin maintains an adequate energy balance by regulating the energy flow and expenditure [15].

Glucose and lipid metabolism are linked together in several ways. There is a crosstalk between melatonin and insulin signaling [75]. Melatonin promotes glucose transport glycogen synthesis, inhibits lipolysis, regulates body weight and glucose metabolism through the phosphorylation of IRS-1 under insulin [56,76]. Membrane-bound melatonin receptors, MT1 and MT2, reduce the intracellular cAMP level and control cAMP-dependent phosphotyrosine

phosphatase activity, thereby accelerating insulin phosphorylation [76]. This process implies strong evidence regarding the protective effect of melatonin by balancing glucose and lipid metabolism. The alteration in the carbohydrate metabolism induced by glucose intolerance and insulin resistance may be reversed by melatonin [77]. It is one of the functions to maintain the energy balance in the heart.

4. Role of Melatonin in Oxidative Stress

In diabetic complications of microvascular and cardiovascular systems, oxidative stress plays a vital role in promoting the disease. Oxidative phosphorylation plays a crucial role in oxidative stress through electron leakage in the form of O_2^-[78], H_2O_2, and HO [79] and triggers apoptosis [80]. Also, the overproduction of mitochondrial ROS triggers hyperglycemia and causes tissue damage [80] by activating nuclear factor kappa B (NF–kB) [81], which further leads to tissue fibrosis, induced by inflammation [82]. Also, excessive ROS disrupts mitochondrial function by activating the release of inflammatory cytokines, growth factors, elastases, and vasoconstrictors [83–85]. These factors activate other ROS sources such as NADPH oxidases, cyclooxygenases, and lipoxygenases, which further increase ROS production in the pulmonary vasculature causing pulmonary vascular endothelial damage [86–88], leading to reduced blood pressure in the heart. A decade ago, Ianas *et al*. first reported melatonin's free radical scavenging activity [89]. It also stimulates the antioxidants to directly neutralize the free radicals, reactive oxygen, and nitrogen species [90]. The hormone can also reduce nocturnal blood pressure [91]. Paul and Simko reported that melatonin guards the heart against ischemia-reperfusion injury through its effective ROS scavenging activity [92].

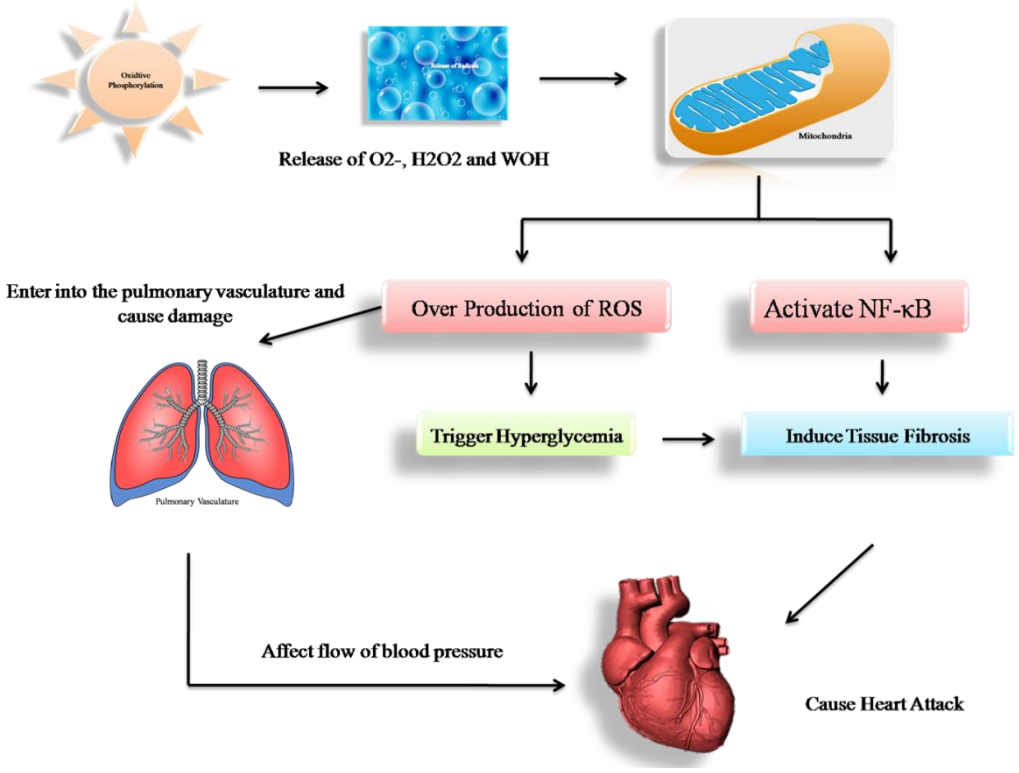

Figure 2. Mechanism of oxidative stress in cardiac function.

Mitochondrial nitric oxide synthase (NOS) plays a vital role in the formation of reactive nitrogen species (RNS), which induces cellular damage and causes cardiovascular risk [93]. The lack of nitric oxide scavenging could adversely affect [94]. The function of mitochondria complex I and IV are influenced by melatonin [95,96]. Melatonin intensifies the activity of

endogenous antioxidative enzymes [97] and neutralizes the nitric oxide, hydrogen peroxide, singlet oxygen, peroxynitrite anion, and hypochlorous acid [90] or directly scavenges NO and ONOO or inhibits the synthesis of NOS [98–100]. Melatonin also stimulates antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and glutathione reductase [90].

The metabolites of melatonin, such as N1-acetyl-N2- formyl-5-methoxy kynuramine and N-acetyl-5-methoxykynuramine, also have a potent antioxidant activity [99,101,102]. Due to scavenging activity on OH, a highly toxic ROS, counteract lipid peroxidation [103,104] (Figure 2). Thus, directly and indirectly, melatonin decreases oxidative stress by antioxidant enzymes and reduces cardiovascular diseases. Overall, it is clear that melatonin and the regulation of circadian rhythm promote cardiac health by reducing oxidative stress.

4.1 The role of melatonin in anti-inflammatory activity correlated with oxidative stress in the cardiovascular system.

In oxidative stress, the H_2O_2 production in human chondrocytes induces the release of IL-1b, IL-8, CXCR-4, TXNIP, STS, and IFI-6-16 [105]. Nian *et al*. reported that the cytokines such as TNFα and interleukin-6 (IL-6) are involved in myocardial ischemic injury and regulate the myocyte survival or apoptosis of the cellular inflammatory response [106]. In cardiac failure, IL-1 signaling plays a negative role by repressing the contractility of the heart, stimulating myocardial hypertrophy, and prompting apoptosis of cardiomyocytes [107].

Some physiological and psychological stresses trigger inflammation leading to chronic inflammatory diseases [108,109]. The overexpression of CXCR4 in cardiomyocytes might stimulate the inflammatory cells, increase TNF-α production, and induce cell death/apoptosis [110]. The activation of CXCR4 interacts with beta-adrenergic receptors and stimulates downstream signaling. CXCR4 plays a critical role in neuro-humoral regulation of the heart and the progression of heart failure [111]. Chronic inflammation may lead to apoptosis and myocardial remodeling [112]. Overall, myocardial damage is further intensified by inflammation (Figure 3).

The expression of specific cytokines (iNOS, COX-2, TNF-α, and IL-6) and pro-inflammatory mediators is coordinated by NF-κB [113]. Though in some instances, NF-κB acts as a cardioprotective mediator, in acute hypoxia and reperfusion injury, chronic activation of NF-κB promotes heart failure through its downstream signals. NF-κB signaling triggers chronic inflammation and pro-inflammatory cytokines release (iNOS, COX-2, TNF-α, and IL-6). It may lead to stress response in the endoplasmic reticulum resulting in cardiomyocyte death [114]. The association between elevated circulating chemokine levels and cardiac dysfunction has been well established [115–117].

Stress modulates the expression of immune response genes through the central nervous system (CNS) via the effects of hormones and neurotransmitters on the gene transcription control pathway [118]. In psychological stress, melatonin suppresses norepinephrine and epinephrine expression levels in rodents [119–122]. In addition, reduced melatonin level leads to elevated oxidative stress and the release of inflammatory mediators. Oxidative stress-mediated cytotoxicity and up-regulation of inflammatory mediators were observed in cases of decreased melatonin levels [112]. The anti-inflammatory effect of melatonin is mediated through counteracting the inflammatory process by free radical scavenging and activation of the endogenous antioxidant defense machinery [123–128].

Melatonin down-regulates the expression of SIRT1, which elicits anti-inflammatory activity [129]. Melatonin blocks hydrogen peroxide-induced phosphorylation of PI3K/Akt,

p38, ERK, JNK, and MAPK and the activation of NF-κB, which is reversed by sirtinol and SIRT1 siRNA. Thus, NF-κB does not directly induce or promote cardiac failure by eliciting the downstream signals. Melatonin decreases the expression of iNOS and COX-2 and also the production of NO and PGE2 [129].

Melatonin has been shown to modulate the immune system by regulating cytokines [130]. Melatonin promotes immune-stimulatory effects on several immune parameters, such as antibody-dependent cellular cytotoxicity [131,132]. Melatonin reduces the synthesis of TNF-α, IL-1β, IL-8 release, and CXCR-4, TXNIP, STS, and IFI-6-16 [129]. Thus, they do not increase the neuro-humoral regulation in the heart and the progression of heart failure. It was reported that melatonin acts as an antioxidant and exerts numerous anti-inflammatory functions [133–137]. In consequence, melatonin plays a critical role in heart neuro-humoral regulation and the progression of heart failure. Melatonin blocks the production of H_2O_2 and exerts its anti-inflammatory activity in maintaining the metabolic activity of the cardiovascular system [138,139]. The aforementioned process implies that melatonin acts as a cardioprotective agent by reducing oxidative stress and inflammatory mediators such as NF-κB.

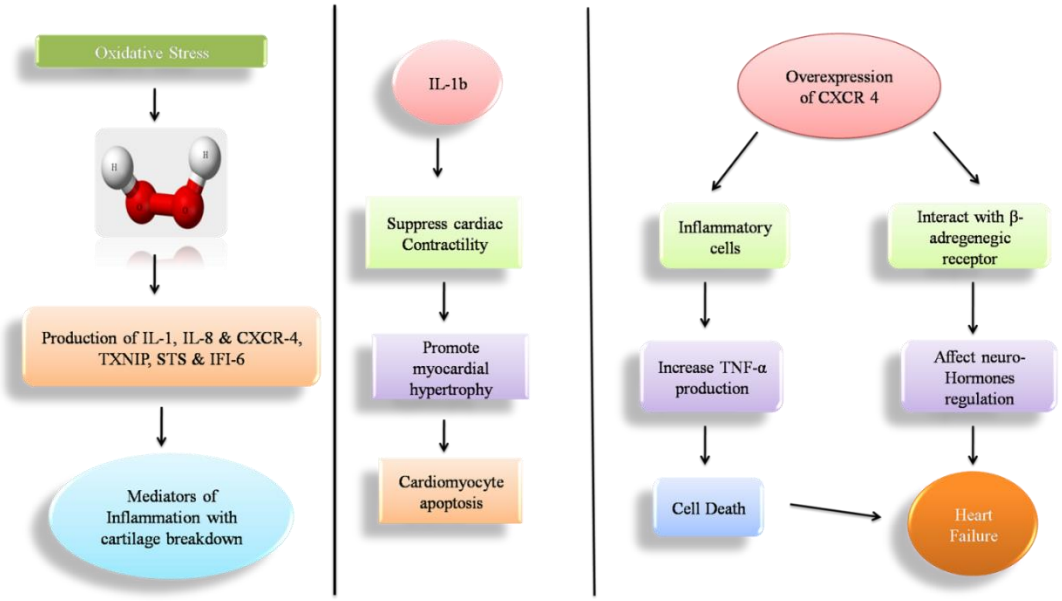

Figure 3. Mechanism of the inflammatory mediator in cardiac function. Overexpression of IL-1b and CXCR4 affect cardiac function leads to cell apoptosis. IL-1b – Interleukin and CXCR4 – Chemokine Receptor 4, TNFα-Tumour Necrosis Factor α

5. Role of Melatonin in DNA Damage Repair

Single-stranded DNA damage-induced response is also involved in heart failure. In general, DNA damage can occur due to metabolic and hydrolytic processes. In the metabolic process, the release of reactive oxygen, nitrogen and carbonyl species, lipid peroxidation products, and alkylating agents cause DNA damage [140,141]. Reports show that ROS causes DNA damage at a frequency of at least 10,000 times per cell per day in humans [142,143].

In the hydrolytic process, the modification of the molecular structure of DNA causes disturbance in the function of the heart as the unpaired DNA single-strand break (SSB) activates DNA Damage Response (DDR) and also the inflammatory cytokine expression through NF-kB signaling [140]. The activation of DDR causes the pathogenesis of heart failure triggered by pressure overload [140] (Figure 4). Minamino *et al.* observed that DDR activation in cardiomyocytes occurs in patients with end-stage heart failure. They also reported that excess pressure causes heart failure in mice [144].

Melatonin protects DNA from damage and oxidation by balancing oxidant-antioxidant balance, inhibiting neutrophil infiltration, and reducing the 8-OHdG level [145]. The hormone plays a pivotal role in maintaining cardiac metabolism. Melatonin stimulates antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSHPx) [146–148], and glutathione reductase (GR) to neutralize or directly scavenge the free radicals [149,150]. Thus, by reducing the DNA damage induced by oxidative stress, melatonin prevents pathological conditions in the heart. Melatonin neutralizes the free radicals causing DNA damage and gives protection through inactivating the DNA damaging agents [151,152]. Melatonin potentiates the DNA repair capacity against strand breaks caused by DNA damaging agents [153,154].

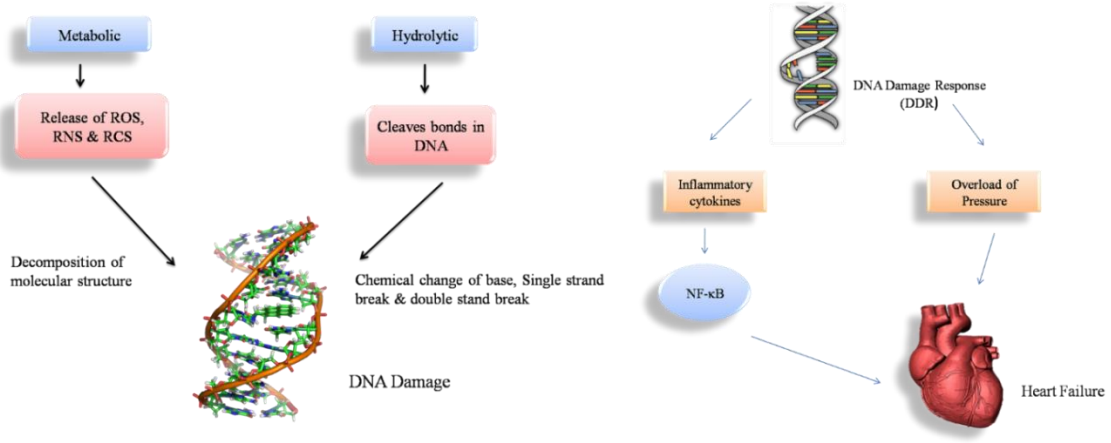

Figure 4. Mechanism of the DNA repair in cardiac function.

6. Hypothesis

Meditation has well been documented to improve cardiac health. Cardiomyocytes derive 80% energy from lipids such as fatty acid and 20% from other sources such as glucose, ketone bodies, etc. Glucose and lipid homeostasis is maintained by circadian rhythm in the heart. Melatonin synthesized from the pineal gland regulates the circadian rhythm. In addition to maintaining circadian rhythm, melatonin also regulates glucose and lipid metabolism.

Melatonin receptors are G protein-coupled receptors with two subtypes, MT_1 and MT_2, regulating glucose metabolism through phosphorylating insulin as crosstalk with insulin and accelerating insulin phosphorylation glycolysis for glucose homeostasis cytoplasm. CoQ neutralizes the free radicals formed during oxidative phosphorylation. Interestingly, the expression of CoQ is regulated by PINK1, whose expresses is dependent on melatonin.

Elevated ROS caused by O_2^-, H_2O_2, and WHO upon entering the pulmonary artery causes pulmonary endothelial damage and reduces the blood flow and blood pressure, ultimately resulting in cardiac dysfunction. On the other hand, the increased production of ROS also causes DNA damage. The DNA damage causes pressure overload and congestive heart failure. Free radicals also trigger the IL-1, IL-8, CXCR-4, TXNIP, STS, and IFI-6, which mediates cartilage breakdown. They also activate the NFκB, which acts as an anti-inflammatory agent, but prolonged exposure causes cell apoptosis leading to a decreased heart size. Melatonin also acts as DNA repairing agent repairing the DNA damage in cardiomyocytes and preventing subsequent inflammatory reactions.

Collectively, melatonin, in addition to being the regulator of circadian rhythm, acts as an antioxidant, anti-inflammatory, DNA repair agent. Further, melatonin also regulates glucose and lipid metabolisms. A number of reports suggest that the melatonin level is increased during

meditation. Independently, meditation has been shown to promote cardiac health. Therefore, we hypothesize that meditation-mediated improvement in cardiac health is through the action of melatonin. (Figure 5).

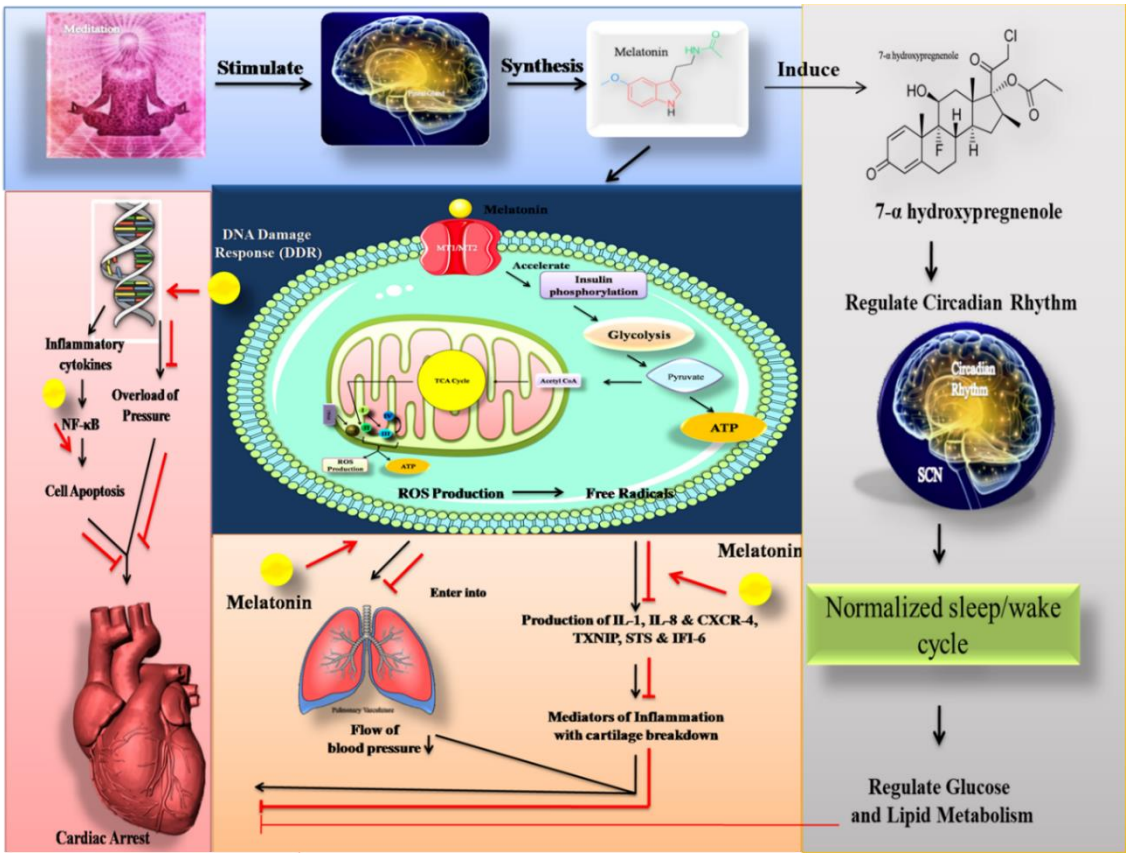

Figure 5. Schematic diagram depicting the possible mechanism of meditation-mediated improvement in cardiac health through melatonin. Meditation stimulates the pineal gland to synthesize the melatonin and subsequent induction the 7-α hydroxypregnenole to regulate the circadian rhythm. The circadian rhythm regulates cardiac glucose and lipid homeostasis. In an altered modern lifestyle, circadian rhythm is disrupted, and consequently, there is a high occurrence of cardiovascular diseases. The altered circadian rhythm with elevated ROS disrupt glucose and lipid homeostasis. The increased level of ROS activates the inflammatory mediators' cytokines and damages the DNA, resulting in altered cardiac physiology. Melatonin is the central player of circadian rhythm, and it protects cardiomyocytes by acting as an antioxidant, anti-inflammatory mediator. Melatonin also repairs DNA damage. The red color refers to the inhibition of the mechanism. MT1/MT2 – Melatonin receptor 1& 2; TCA – Tricarboxylic acid; ROS – Reactive Oxidative Species; IL-1, IL-8 – Interleukin 1& 8; CXCR – Chemokine receptor; TXNIP - Thioredoxin Interacting Protein; STS – Steroid Sulfatase; IFI-6 – Interferon 6; NF-κB - Nuclear Factor kappa-light-chain enhancer of activated B cells. Red color lines indicate inhibition. The blue color background implies meditation regulates melatonin. The brown color background implies a Circadian rhythm. Dark blue implies – Mitochondrial function (Glucose and lipid metabolism and Antioxidants). Light Orange color implies – Anti-inflammatory. Light pink color Implies – DNA Damage.

7. Conclusions

Sleep and cardiovascular connection are two-way lanes. With heart disease, someone might have other health issues, including sleep disorders. Likewise, heart disease signs may worsen by sleep issues, such as obstructive sleep apnea (OSA) and insomnia. It is necessary to sleep a decent night, whether or not your heart is stable. Sleep improves both the heart and energy, thought abilities, and fitness. People will feel more pressure from the core if they are willing to cope with the sleep issues.

Owing to the frequent rising of sleep apnea patients, they have inadequate quality sleep and remain tired all day long. They may have impaired cardiovascular function as well. Sleep dysfunction is 47-83 percent, 35 percent, and 12-53 percent of those with coronary disease, auric fibrillation (heart rhythm disturbances, and stroke). The cardiac condition is exceptionally susceptible. Researchers report that sleep apnea that is not treated is one to five times more likely to die from heart failure. The meditation on sleep is a rare, directed experience that provides all-around sleep relief alone and helps us let go of the day — all that happened and all that was said — to relax the mind while relaxing the body at the same time. Scientifically speaking, meditation helps decrease the heart rate by ignition and relaxing breathing, improving the chances of a quality night's sleep.

Cardiovascular diseases (CVD) are increasing the risk factor worldwide. Nowadays, yoga and meditation pay considerable attention to the defense of CVD. But the scientific mechanism of meditation behind CVD protection was not known. Meditation strategies have been documented to improve some amounts of HPA. Data from the American Journal of Practice were taken from the report. Studies have shown that melatonin impacts ischemia-reperfusion, transient myocardial hypoxia, pulmonary hypertension, elevated blood pressure, valvular cardiac failure, artery disorders, and lipid metabolism.

Although melatonin's function in the sense of heart failure has been studied in a few clinical trials, recent laboratory research results support the possible usage of melatonin in heart failure as preventive and adjunctive curative therapy. Melatonin could be a promising treatment alternative for cardiovascular disorders as cheap and well-accepted medicine. Recently several reports suggested that the continuous practice of meditation increases the production of melatonin, a hormone. Based on these, we derived the plausible meditation mechanism, which protects the heart from CVD. In these, we revealed the connection between meditation and melatonin and the role of melatonin in cardiovascular protection. Melatonin regulates the circadian rhythm, but it can also act as an anti-inflammatory, antioxidant agent and have a role in glucose and lipid homeostasis and DNA repair mechanisms because these are the reason which leads to cause cardiovascular diseases. Melatonin, which produces during the night only due to the modern lifestyle, decreased melatonin production. Recently shreds of evidence from the science community revealed melatonin production during the meditation. Thus, we conclude that melatonin production during meditation protects the heart from CVD. Further, we need to prove our hypothesis in real-time experiments.

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Conflicts of Interest

The authors declare no competing financial interest and no conflicts of interest.

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