Review

The therapeutic potential of melatonin against hepatotoxicity caused by obesity and NSAIDs: A comprehensive review

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ABSTRACT

The obesity and increased free fatty acid level are considered the etiology of hepatotoxicity leading to steatohepatitis and hepatic fibrosis. Obesity promotes inflammatory response and oxidative stress. Adipocytes secrete various proinflammatory cytokines including TNF-α, IL-1β, IL-6 and leptin to initiate a vicious cycle and cause further fat accumulation and weight gain. Specifically, to liver, the fat accumulation will cause non-alcoholic fatty liver disease (NAFLD), the most prevailing chronic liver ailment, if it is not properly treated, then it will cause severe outcomes including fatality. In addition, obesity also cause other inflammatory disorders including osteoarthritis of the knee, joint pain, etc. Non-steroidal anti-inflammatory drugs (NSAIDs) are most often used medicines for treatment of inflammation but their serious side effects are concerning. These include gastric mucosal damage, liver injury with elevated aminotransferase (AST/ALT) levels, hepatitis, jaundice and more fatal liver diseases. Melatonin, an antioxidant and anti-inflammatory molecule can be used to treat diverse kind of inflammatory diseases. It remarkably reduces the mRNA levels of pro-inflammatory cytokines of TNF-α, IL-6, IL-1β, etc. Melatonin and its metabolites retain the properties as an effective free radical scavenger and regulate various antioxidative and pro-oxidative enzymes. This molecule can potentially abate the ill effects of hepatotoxicity induced by both NSAIDs and obesity. Therefore, this review briefly summarizes the recent available knowledge on the protective effects of melatonin against various disorders involving weight gain and hepatotoxicity.

Key words: Obesity, metabolic syndrome, NSAIDs, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), melatonin, hepatotoxicity, oxidative stress.

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1. INTRODUCTION

Obesity and its complications have become a global health problem. Transitioning to urbanization, westernized lifestyles including diets with high-calorie, consumption of increased fat and sugar-rich foods, and low levels of physical activity have caused a large population with health hazards (1). These include non-alcoholic fatty liver disease (NAFLD),

hyperlipidemia, type 2 diabetes, hypertension, cardiovascular diseases (CVDs). All of these result in raising mortality in population (2). Among them, NAFLD is caused by the insulin resistance, long-term consumption of a high fat diet, obesity, dyslipidemia, oxidative stress which lead to hepatic lipid accumulation and hepatic apoptosis (3, 4). The increasing prevalence of obesity associated with NAFLD currently affects a quarter of the population of Asian origin, and the number has increased gradually in the past two decades (5). Obesity also causes mechanical forces to the joints due to heavy weight. Consequently, it has become the main cause of osteoarthritis, and other kinds of arthritis including joints of hip, spine, knee, ankle (6).

Non-steroidal anti-inflammatory Drugs (NSAIDs) are frequently prescribed for pain associated with inflammation. Long-term use of these drugs causes even more hepatic damage in the patients (7) with chronic pain and inflammation. The prime causative factor behind obesity and weight gain is the consumption of a diet rich in fat (8). Obesity causes visceral fat accretion and hastens low-grade, chronic inflammation, further activating inflammatory pathways crucial for developing diverse of inflammation associated diseases (9). Extended NSAIDs use and their metabolites extracted on the intestinal mucosa due to enterohepatic circulation cause topical damage of the intestinal barrier, therefore, promoting the bacterial translocation and related baleful substances enter the portal circulation, generating endotoxemia. This commences an inflammatory response in the liver, effectuating non-alcoholic steatohepatitis (NASH) (10).

Melatonin poses multiple biological effects, which can be a positive alternative against NASH. It can protect against various metabolic syndrome complications. Therefore, melatonin can be used for a variety of disastrous diseases (11) based on its antioxidant capacity (12). It not only directly scavenges free radicals but also activates other antioxidant enzymes by regulating their gene expressions (13). The protective roles of melatonin in lipid metabolism, reducing body weight, modulating glucose metabolism, and insulin sensitivity have been well documented (14-16). It has ameliorative effects against high fat diet-induced NAFLD (17). In this review, we focus on discussing the protective role of melatonin on obesity and NSAID-induced hepatic damage.

2. OBESITY AND ITS ASSOCIATED PATHOLOGIES

World Health Organization (WHO) defines overweight or obesity as abnormal with excessive accumulation of fat and is unhealthy. Even Asian and Western populations have marked differences in their lifestyle, eating habits, genetics, and body composition, central obesity is markedly associated with metabolic syndrome (5). Asians, in particular, are more susceptible to central fat deposition or android obesity despite having a lower BMI than their Western counterpart. Notably, about 8-19% of the Asian populations having BMI < 25 kg/m^2, that is, the non-obese population, are found to have NAFLD, referred as lean or non-obese NAFLD. Also, the increasing prevalence of obesity in children and adolescent populations in developing and developed countries is becoming very distressing as it is affecting both the physical and mental health of the upcoming generation (18). The combined effects of some aspects, like lack of physical activities, epigenetic modifications, genetic polymorphisms, and insulin resistance on both the endoplasmic reticulum and oxidative stress, increase in accumulation of lipids in the hepatocytes, leading to steatosis (19). Furthermore, the presence of excessive fat in daily diet modifies the gut microbiota and increases fat storage in the gut. This alteration of gut flora causes NAFLD by a) damaging tight junctions increases intestinal permeability for bacteria and other toxins b) increasing body weight, insulin resistance, lipogenesis, fibrogenesis elevate oxidative stress in liver (10).

2.1. Obesity-driven hepatic damage.

Obesity is a risk factor for the progress of NAFLD as, at least, 5% of adults or children who are overweight and 20% of obese are suffering from NASH (20). Obesity causes low-grade inflammation and subsequent insulin resistance, which ultimately leads to increased release of free fatty acids (FFA) from the adipose tissues. FFAs, the principal substrate for intrahepatic triglycerides, are obtained not only from adipose tissue lipolysis (approximately 60%) and diet but also from de novo lipogenesis within the hepatic cells. A diet composed of excessive carbohydrates and fat naturally prompts the commencement of hepatotoxicity. Additionally, mitochondrial defects, endoplasmic reticulum (ER) stress, and oxidative stress occur within hepatic damages connected with glucotoxicity and lipotoxicity (21). The dysfunctional and insulin-resistant adipocytes release FFAs, accelerating lipotoxicity by accumulating triglyceride-derived toxic metabolites. Several inflammatory pathways, lipoapoptosis, and mitochondrial dysfunction affect the normal function of hepatocytes and their ability to dispose of excess FFAs, leading to NASH (19). Thus, obesity becomes the main causative factor behind NAFLD including hepatic steatosis ranged from simple steatosis (SS) to non-alcoholic steatohepatitis (NASH). These disorders may progress to hepatic fibrosis, liver cirrhosis and hepatocellular carcinoma (22).

Steatohepatitis sparks a fibrogenic response, bringing about collagen deposition and hepatic nodularity. Both alcohol consumption and obesity predispose such conditions (23). During fibrogenesis, immune cells crosstalk with wound-healing cells including myofibroblasts, activated endothelial cells, and progenitor cells and they are managed to target tissue regeneration following liver injury. Under normal conditions, damaged hepatocytes are either replaced or subjected to apoptosis, when this mechanism fails, it leads to obesity, fibrosis, scarring, and cirrhosis (24, 25). Several studies indicate that fat mass and obesity-associated gene (*FTO*), or alpha-ketoglutarate-dependent dioxygenase, the first gene associated with obesity, is located at chromosome 16. Overexpression of this *FTO* gene in the L-02 cell line of hepatocytes is associated with enhanced lipogenesis and oxidative stress characterizing NAFLD, thus oxidative stress being the principal cause behind accretion of lipids in the liver, pathogenesis of NAFLD and other associated disorders (26).

2.2. Obesity-induced inflammation and oxidative damage.

Adipocytes are considered endocrine organs as they can produce many mediators of insulin resistance and pro-inflammatory cytokines which are closely associated with increased incidences of cardiovascular diseases (CVDs), diabetes *mellitus*, and other ailments (27). The production of ROS and adipogenesis are also closely related (28). Low-grade inflammation, as seen in obese patients with enhanced plasma levels of C-reactive protein, IL-6, TNF-α, MCP-1, and osteopontin, may be the main factor behind obesity-related pathologies (29). A decrease in adiponectin levels, another hormone from adipose tissue having insulin-sensitizing action in obesity, contributes to insulin resistance (30). Leptin, a hormone predominantly produced by adipocytes and released in the bloodstream (31), is the key regulator of hunger and satiety to inhibit food intake by triggering the leptin receptor (OB-Rb) on the hypothalamus thus, exerting an anti-obesity effect (32-34). However, most of the obese patients are resistant to leptin and unable to respond to signals of leptin (35-38). On other hand, this cell signaling molecule elevates the ROS formation in the endothelial cells in an oxygen-dependent manner, actuating the synthesis of NF-κB. This links to enhanced expression of MCP-1 (monocyte chemoattractant protein-1), which plays a vital role in inflammation (39-40). NF-κB promotes the expressions of enzymes including COX to synthesize various prostaglandins and iNOS to generate nitroxide. All of these are mediators

of inflammation (41). Oxidative stress and an imbalance in anti and pro-apoptotic proteins in the Bcl-2 family commit to hepatocyte apoptosis in the pathophysiology of NASH. C-Jun NH2-terminal kinase (JNK) is upregulated in high-fat diet-induced NASH, so does the Bax, an apoptosis regulator (42). Moreover, cytokines play a chief role in regulating hepatic lipid accretion and the progression of NAFLD. When the immune system cannot balance the excessive pro-inflammatory cytokines, it thus results in ROS production and lipid metabolic disorder (43). Excess of ROS generation in the cell membrane furthermore increases the release of tumour necrosis factor-alpha (TNF-α) in adipose tissue, Kupffer cells, etc. Adipocytes also produce polypeptides like plasminogen activator inhibitors (PAI-1) and TNF-α (44). TNF-α is a major pro-inflammatory cytokine to induce liver damage and metabolic disorders.

2.3. Obesity and oxidative stress.

Obesity is associated with oxidative damage and inflammation (46). Obesity-induced inflammation-related pathways can increase reactive oxygen species (ROS) production (46-48). Oxidative stress is the imbalance between ROS and antioxidants with excessive ROS production (49). There are enzymatic and non-enzymatic antioxidant systems of which Vitamin E, vitamin C, carotenoids, uric acid, and polyphenols, are a part of the non-enzymatic antioxidants. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) are three of the key antioxidant enzymes (49-50). Oxidative stress can damage lipids, proteins, and DNA, resulting in a loss of biological activities and homeostasis. This can be manifested as oxidative damage to cells and tissues (49). Furthermore, oxidative stress can initiate or exacerbate an inflammatory response by destroying cell structures (48). Therefore, for the proper functions of different organs it requires a balance between oxidants and antioxidants (49). One of the cellular responses to an excess of fat in obesity is an increase in the generation of ROS (46, 47, 51). A persistent imbalance in energy metabolism with excessive food consumption, obesity, and physical inactivity also contribute to inflammation and increased ROS generation, which in turn causes mitochondrial malfunction (52, 53). Bonnard *et al.* (54) demonstrated that a high-fat, high-sucrose diet induces ROS generation and mitochondrial alterations in mice muscle tissue. According to Freeman *et al.* (55), diet-induced obesity enhanced the generation of ROS in the prefrontal cortex and hippocampus of the brain. In rats, high-fat diet-induced obesity increased oxidative damage and mitochondrial dysfunction in the brain and plasma (56). Additionally, increased fat tissue considerably decreased the activity of antioxidant enzymes like SOD, CAT, and GPx (47). In vascular tissues of diet-induced obese mice, Chen and Stinnett (57) demonstrated that a high-fat diet stimulated NADPH oxidase, which is a generator of ROS and mediated the development of toll-like receptors (TLR). Marchesi *et al.* (58) found enhanced superoxide generation and NADPH oxidase activity in the perivascular adipose tissue of obese New Zealand mice. Excessive ROS generation and inflammation may result in mitochondrial malfunction (59). Additionally, excessive food intake and obesity cause mitochondrial alterations that increase the production of ROS and oxidative stress (47, 60, 61).

3. NSAIDS

The most frequently used drugs are NSAIDs, which include various compounds with analgesic, antipyretic, and anti-inflammatory effects (62). In the year 1899, Aspirin or acetylsalicylic acid, the first NSAID, came into the market (63). NSAIDs like indomethacin and ibuprofen were introduced subsequently in 1964 and 1969 (64). Since then, several other compounds with similar therapeutic effects came into the market, which are various classes

of organic acids (63). NSAIDs are widely used in patients of various chronic conditions including rheumatoid (64) and osteoarthritis (65). Apart from these, patients of juvenile and psoriatic arthritis, rheumatic fever, Reiter's syndrome, systemic lupus erythematosus, pericarditis, gout, Kawasaki disease, ankylosing spondylitis, dysmenorrhea, etc. are frequent users of NSAIDs (66). As NSAIDs act by inhibition of cyclooxygenases, they may be classified as selective or non-selective inhibitors. Selective inhibitors primarily inhibit cyclooxygenase 2 (COX2), known as COXIBs but not the cyclooxygenase 1 (COX1). This minimizes their serious side effects as other NSAIDs (67) which are listed in table 1.

Table 1 The side effects of NSAIDs on different organs

Organs	**Side effects of NSAIDs**
Gastro-intestinal tract	The acidic property of NSAIDs commences mucosal damage. The NSAIDs are dissociated into an ionized form in the gastric ambiance due to the strong acidic environment. After their relocation into surface of epithelial cells, where they entrap hydrogen ions that induce topical mucosal injury. The use of Non-selective NSAIDs (inhibiting both COX 1 and COX 2) is known to cause perforations, bleeding, and ulceration (68). A prior history of perilous ulcers and older age (> 70 years) are the two important risk factors for GI events. (69)
Cardiovascular system	The use of non-selective NSAIDs is linked with an increased risk of various cardiovascular events, which are probably associated with manifold mechanisms, including nitric oxide production, endothelial function, volume retention, blood pressure, and oxidative damage. NSAIDs like rofecoxib raise the susceptibility of the cardiac cell membrane to oxidative damage (70).
Renal system	Prostaglandins are concerned with the maintenance of vascular tone, renin release, and controlling tubular function. The use of Nonselective NSAIDs inhibit both COX1 and 2 that leads to a brief imbalance in water and electrolytes. Inhibition of COX 2 by NSAIDs induces sodium retention in elderly patients, whereas COX 1 inhibition is known to cause decreased GFR. Inhibition of PGI2 and COX2-mediated prostacyclin synthesis causes increased potassium secretion in the distal tubule (71).
Hepatic system	NSAIDs are metabolized in the liver and have high bioavailability and binding capacity to plasma proteins. NSAIDs and salicylates undergo metabolism in the hepatic tissues by CYP450 enzyme systems. A hepatotoxic intermediate N-acetyl-p-benzoquinone imine (NAPQI) is found to increase in patients with decreased glutathione stores in the body. Thus, these drugs should be used carefully in patients with advanced liver diseases (72).

3.1. Mechanisms of NSAIDs.

In 1971, Vane and Piper demonstrated for the first time that NSAIDs produce their effects by the way of inhibition of prostaglandin as well as prostanoid biosynthesis by COX (Cyclooxygenase) enzymes (73). Arachidonic acid, an unsaturated 20-carbon fatty acid ingrained as a phospholipid ester in the cell membrane, is the precursor for prostaglandin. Free arachidonic acid is released as a result of various kinds of stimuli and is eventually transformed into lipid intermediators collectively referred as eicosanoids by the COX and

lipoxygenase (LOX) enzymatic pathway (74). Two isoforms of COX were discovered in the late 1980s: COX-1 and COX-2, of which COX-2 is known to produce the prostaglandins responsible for the impression of pain and inflammation. COX-1 are known to produce protective prostaglandins, which are accountable for the normal functioning of platelets and gastrointestinal mucosal integrity and cytoprotection (75, 76). The use of non-selective NSAIDs poses a greater risk as inhibition of COX-1 causes loss of GI mucosal integrity and thus leads to incidences of menacing GI ulceration, perforation, and bleeding (77). For this reason, nowadays, selective COX-2 inhibitors or COXIBs are discovered after separating the COX-1 and COX-2 pathways and targeting only the latter.

4. NSAIDS INDUCED HEPATOTOXICITY

NSAIDs are known to directly damage the liver as the use of diclofenac, sulindac, nimesulide, etc., may cause terminal liver injury (78, 79). Sulindac and diclofenac are associated with hepatotoxicity as their active metabolites, like N,5-dihydroxy diclofenac, are cytotoxic (80, 81). Problems in the liver functioning alter the metabolic processing, rendering damage to other organs like GI mucosa and kidney (described in Table 1) (82, 83). Apart from hepatotoxicity, jaundice, hepatic failure, etc., some of the patients on NSAID therapy are asymptomatic but with the hepatic damage. Discontinuation of use within 4-8 weeks will let the liver function back to normal even after long-term use, but some will develop to acute liver failures, a potentially fatal condition (84-87).

4.1. Hepatic metabolism of NSAIDs and its baneful products giving rise to oxidative stress and inflammation.

NSAIDs foster ROS generation by inducing uncoupling of oxidative phosphorylation and causing partial reduction of oxygen by hampering the electron transport chain. NSAIDs like indomethacin are even found to adhere to a site nearby complex 1 and ubiquinone, resulting in the generation of ROS (88, 89). ROS, which can act as a biological signal of cellular responses, is generated in all mammalian cells as a result of the normal metabolism or due to the triggering of oxidative enzymes as a kickback mechanism to exogenous stimuli while excessive accumulation of ROS causes oxidative damage to the cells (90, 91). Examples of ROS/RNS include superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$), Nitric oxide ($NO^{\bullet}$), peroxynitrite ($ONOO^-$), etc. Free radicals have immense potential to react with and are detrimental to DNA, protein, and lipids (92). Majority of the $O_2^{\bullet-}$, H_2O_2, and OH· are generated in the mitochondria from the electron transport chain (ETC). ETC locates on the inner mitochondrial membrane and contains iron and copper complexes that may catalyze further reactions between $O_2^{\bullet-}$ and H_2O_2 to disrupt mitochondrial proteins (93). The central role of the liver in xenobiotics and drug detoxification make it expose to ROS (94) and various endotoxins generated by bacteria (95). These factors induce production of TNF-α and anti-inflammatory cytokines like IL-10 (96). Three main mechanisms that spark the incidence of ROS-mediated hepatic damage include a) lipid peroxidation in the cellular membranes, b) apoptosis induced by a transmembrane protein, Fas ligand (FasL), a member of the tumor necrosis factor family, and c) cytokine induction.

The products of ROS including malondialdehyde (MDA) and 4 hydroxyenal also hinder normal cellular functions and play the pivotal roles in fibrogenesis of hepatic tissue (97-99). Aldehyde products of lipid peroxidation activates NF-kB to increase the production of pro-inflammatory cytokines. Adhesion molecules, including TNF-α, E-selectin, and adhesion molecule 1, are also activated by ROS (17). Therefore, oxidative stress is involved in the etiology of NAFLD. Management of antioxidative enzymes is an important treatment

approach, and it is beneficial for lowering the occurrence and progression of NAFLD (100, 101).

4.2. Mitochondrial damage by NSAIDs.

Mitochondrion is the powerhouse of the cell, it is the body's principal site for ROS and oxidative phosphorylation (102). NSAIDs can impede several complexes of the electron transport chain of mitochondria. For example, indomethacin and diclofenac can obstruct rotenone-sensitive complex I activity and eventually increase the production of $O_2^{\cdot -}$, which further promotes the formation of other harmful oxygen radicals (103). Diphenylamine, an usual component in NASIDs, when incubated with freshly isolated hepatocytes, caused mitochondrial swelling, reduced mitochondrial membrane potentials, uncoupling of oxidative phosphorylation and altered ATP content in the hepatocytes by generating ROS, oxidation of NADP and protein thiols (104, 105). Diclofenac, the most commonly used NSAID, damaged inner mitochondrial permeability transition pore (MPTP) caused an increased ROS, oxidation of protein thiols, NADP, and mitochondrial swelling in hepatocytes leading to hepatotoxicity (106). A loss of mitochondrial membrane potential due to increased MPTP opening impairs ATP synthesis, which directly causes osmotic cellular shock. In addition, the increased MPTP opening facilitates the release of proapoptotic factors of cytochrome C (CYT C) (107), apoptosis-inducing factor (AIF) (108) and loss of homeostasis and cell integrity, finally resulting in necrosis (109). Another interesting hypothesis indicates that inhibition of COX 2 by NSAID blocks prostaglandin E2 (PGE2) synthesis and results in bile acid-induced apoptosis and liver damage. PGE2 superintends Bcl-2, a mitochondrial protein with antiapoptotic functions and can regulate cell death by inhibiting or inducing apoptosis (110).

5. MELATONIN AS A NOVEL AND EFFICIENT PROTECTIVE MOLECULE

Melatonin was isolated for the first time in 1958 by Lerner *et al*. (111) from the bovine pineal gland and is an important biological regulator of the sleep-wake cycle. It is synthesized from the amino acid tryptophan (112) with both hydrophilic and hydrophobic nature. It is a small size antioxidant and can diffuse between the cell compartments, thus proving itself as a better antioxidant than vitamins E, C, and glutathione. This indolamine consequently defends the cell from excess ROS/RNS with a substantial role in aging and diseases (113). The favorable sub-cellular distribution of melatonin profoundly impacts its free radical scavenging activity (114-115).

Melatonin affects energy metabolism, attenuating oxidative stress, body weight gaining, fat deposition, and inflammatory responses in mice (14-16). NAFLD is caused by fatty accumulation in the liver, which leads to hepatic steatosis. Metabolic syndromes like hyperlipidemia, obesity, and diabetes are closely associated with this condition (116, 117). Currently, the relationship between circadian disruption, glucose metabolism, and other components of the metabolic syndrome has been addressed since the circadian system is one of the major regulators of human health and metabolism. It regulates gene expression, release of various hormones, body temperature, activity pattern, energy expenditure, and other important functions (118). It has been found that in pinealectomized rats, loss of melatonin levels, increased deposition of triglycerides in the liver as well as hyperinsulinemia while prolonged administration of melatonin restored insulin sensitivity and improved lipid metabolism in these rats (119).

5.1. Melatonin on hepatoprotection.

The most prevalent chronic liver disease in Western countries today is NAFLD which may some extent relate to circadian disturbance (120). The circadian rhythm governs oxidative stress, inflammation, hepatic triglyceride buildup, and mitochondrial dysfunction which are linked to metabolic homeostasis (121). These factors all have the roles in the pathophysiology of NAFLD. Melatonin is considered as a circadian regulator and a potent antioxidant (122, 123), which are crucial for the maintenance of circadian rhythm of liver as well as its structure and function. It has potential to inhibit lipid peroxidation and pro-necrotic oxygen radical load, thus can acts as a beneficial agent against NAFLD-induced oxidative stress and apoptosis in hepatocytes. Melatonin treatment significantly reduced hepatic cytosis and hepatic lesions induced by carbon tetrachloride toxicity compared to untreated group (124). Liver damage can be alleviated by reducing the oxidative stress, which improves liver histology in rats, as shown in melatonin treated high-fat diet-induced NAFLD. The lipid peroxidation (17) serum cholesterol and triglyceride levels are decreased in mice NAFLD model with administration of melatonin (125, 126). Melatonin alone or combined with pentoxifylline, an anti-haemorrheologic, or pioglitazone, a drug used to treat type 2 diabetes in NAFLD animal models revealed its therapeutic effects (127, 128). In humans, melatonin is well established as an antioxidant and a candidate drug for NAFLD. It was found that after 24 weeks of treatment with melatonin, in patients with NAFLD, levels of aminotransferases of AST and ALT decreased as compared to their pretreated levels (129).

5.2. Effect of melatonin on oxidative stress and inflammation.

Proinflammatory cytokine IL-6 is associated with the pathogenesis of inflammatory diseases. IL-6 activates glycoprotein (GP) 130 monomer, which effectuates the commencement of the Jak (Janus kinases)/STAT signaling pathway, a potent driving force behind various inflammatory conditions. IL-6 with IL-1 and TNF-α plays a critical role in the maintenance of inflammatory diseases (130). Melatonin has a key role in inhibiting inflammatory pathways by promoting liver regeneration through the signaling of IL-6/GP130-STAT3 (131). The inflammation stimulates the progression of NAFLD to NASH and melatonin has the beneficial effects on mRNA levels of proinflammatory markers of mitogen-activated protein kinases (MAPK) signaling (132). Damage of mitochondrial aconitase enzyme by ROS produced by NSAIDs leads to the release of free iron from the iron-sulfur cluster, which then reacts with H_2O_2 to produce hydroxyl radical to trigger oxidative stress. Silent information regulator transcript 1 (SIRT1) is a NAD^+-dependent deacetylase that inhibits NF-κB and curtails the extent of inflammation and levels of oxidative stress (133). NSAIDs are known to inhibit SIRT1, which modulates different operations involving senescence, inflammation, apoptosis, and deacetylating histones and nonhistone proteins. Melatonin imposes its anti-inflammatory effect by inhibiting NF-kB translocation to the nucleus and binding to DNA. Therefore, this process reduces production of proinflammatory chemokines, cytokines, and expression of adhesion molecules. Additionally, melatonin also suppresses the enzymes responsible for generating prostaglandins and reactive oxygen species (134, 135). In mice treated with high fat diet (HFD) melatonin lowered their expression of mRNA levels of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6 compared to only HFD group. Obesity-associated inflammatory cytokines are known to play a crucial role in several acute and chronic liver diseases. The levels of total c-Jun N-terminal kinases (JNK), phospho-JNK (p-JNK), total P38, and phospho-P38 (p-P38) in liver tissue indicated notable differences in the melatonin-treated and untreated group indicating the beneficial effects of melatonin. Thus, melatonin

can potentially ameliorate hepatic pathologies related to NAFLD, decreasing inflammation via the MAPK-JNK/P38 signaling pathway (14). A significant increase in levels of glutathione (GSH) and a decrease of MDA levels in liver tissues were observed in HFD fed animals treated with melatonin (5-10 mg/kg) which indicated abatement of oxidative stress and subsequent liver damage from NAFLD (17). Treatment with melatonin also decreased the expression of peptide hormone retinol-binding protein (RBP4), improved insulin resistant glycemia, reduced ER-mitochondrial distance, and reversed macrosteatosis to microsteatosis at hepatic pericentral zone in obese mice (136).

5.3. Mitochondria as the therapeutic target of melatonin in obesity and its associated disorders.

Mitochondrial malfunction is the underlying cause of insulin resistance and related metabolic disorders (137). While most research on the interaction between insulin resistance and mitochondrial dysfunction has been conducted on skeletal muscle (138), new findings indicate that hepatic mitochondrial dysfunction may also be involved in the development of insulin resistance (137) and liver steatosis (139). Hyperglycemia causes various alterations in the hepatic mitochondria including impaired oxidative phosphorylation, elevated ROS, and ultrastructural aberrations (140). Alternatively, the consumption of drugs for treating various illnesses like type 2 diabetes, obesity, and aging can also cause mitochondrial dysfunction (141). More evidence showed the positive effects of melatonin to reverse the damage and improve liver functions in obesity-associated diabetes (142). According to a new evolutionary theory put forth by Tan *et al*., the mitochondrion is the original sites of melatonin synthesis in eukaryotic cells, and the locally synthesized melatonin is the mitochondrial targeted antioxidant (143). It builds up against a concentration gradient in mitochondria at an extremely high level. This is most likely accomplished by active transit through the melatonin transporter(s) in the mitochondria. By scavenging ROS, blocking the mitochondrial permeability transition pore (MPTP), and activating uncoupling proteins (UCPs), melatonin protects mitochondria from the oxidative stress. Melatonin, therefore, preserves mitochondrial functioning and the optimum potential of the mitochondrial membrane (144). Agil *et al.* (145) observed a strong correlation between diabetic-induced liver steatosis with glycogen storage and mitochondrial dysfunction in mice and the abnormalities in mitochondria were frequently linked to oxidative stress in hyperglycaemia or persistent consumption of a diet rich in fat. It also appears that melatonin interacts with mitochondrial ETC complexes I and IV to enhance electron flow and raise ATP generation in baseline conditions (146, 147). It was hypothesized that melatonin's high redox potential (~0.98 V) might aid in electron transport in the ETC by contributing an electron to complex I (148, 149). Nevertheless, several studies have reported the function of melatonin in mitochondrial metabolism, particularly oxygen consumption (150-152).

6. MELATONIN AND ITS EFFECTS ON NSAIDS

Melatonin directly impacts the cells and tissues that are a part of the inflammatory response, which allows it to regulate the inflammatory process. Melatonin has been shown to suppress the expression and activity of crucial enzymes involved in the inflammatory process, such as phospholipase A2, 5-lipooxygenase, and cyclooxygenase 2, by acting on its high-affinity (pM-nM) specific receptors, either G-protein coupled MT1 and MT2 in the plasma membrane or nuclear (ROR/RZRb)-binding sites, present in macrophages, lymphocytes, and other cells (153). The basic action of NSAIDs is to inhibit synthesis of prostaglandin, which is omnipresent intracellularly and to regulate body temperature and

sleep directly (154-155). NSAIDs including aspirin and indomethacin can disrupt sleep and melatonin levels in the blood due to their relevant action since prostaglandins are mediators of sleep and wakefulness (156). Several studies from the past few decades indicated that prostaglandins are the arbitrator of the sleep-wake cycle, as prostaglandin D2 is involved in sleep induction and E2 in wakefulness. Thus, it is obvious that inhibition of prostaglandin synthesis by NSAIDs will disrupt the circadian rhythm and alter sleep patterns (157). Prostaglandins notably increase the synthesis of melatonin, and thus, some NSAIDs like aspirin, ibuprofen, etc., disturb the normal sleep pattern in healthy subjects (158). Lumiracoxib and its metabolite 4'-hydroxylumiracoxib (M5) have the potential for binding covalently with proteins to diminish GSH levels, and brings about oxidative stress and liver injury (159). The decrease in GSH levels was notably prevented by melatonin supplementation, thus proving to be a promising protective molecule (160). The protective mechanisms of melatonin on NSAIDs and obesity associated oxidative stress have been summarized in the Figure 1.

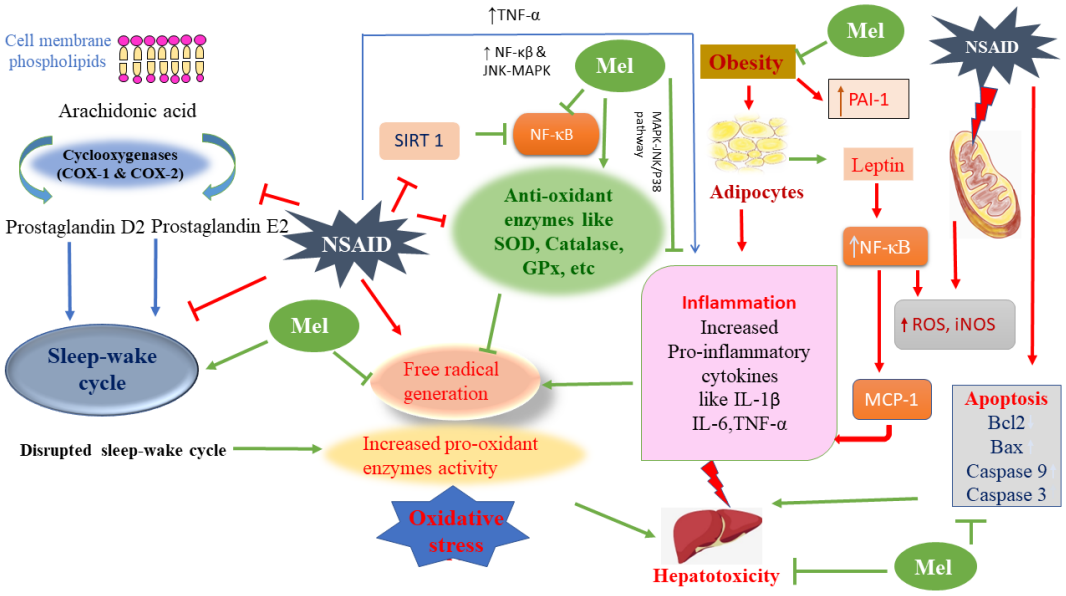

Fig. 1. Protective mechanisms of melatonin in safeguarding the adverse effects of NSAIDs and obesity-induced oxidative stress

NSAIDs, or Non-steroidal anti-inflammatory drugs, inhibit the enzyme cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). As a result, the synthesis of prostaglandin (PGs) is obstructed, which causes disruption of the sleep-wake cycle and thus the release of free radicals and oxidative damage. Antioxidant enzymes like SOD, catalase, GPx, etc. are inhibited by NSAIDs. Also, pro-inflammatory cytokines are increased coincidentally. NSAIDs and their metabolic products cause direct damage to hepatocytes. Obesity, on the other hand, gives rise to metabolic syndrome like diabetes, hyperlipidemia, atherosclerosis, etc., which stimulates inflammatory pathways. Free fatty acids accumulate in the hepatic tissues, causing fatty liver. Adipocytes or fat cells have a chief role in the production of hormones like adiponectin, resistin, and leptin, which again promote the release of pro-inflammatory cytokines and initiation as well as the advancement of NAFLD to steatosis and fibrosis. Leptin enhances NF-κB levels and thus MCP-1 or monocyte chemoattractant protein-1 which is directly linked to inflammation. Adipocytes increase the release of plasminogen activator inhibitor-1 (PAI-1) and TNF-α. These regulate inflammation through autophagy modulation. Melatonin modulates the MAPK-JNK P38 pathway to inhibit the increase of proinflammatory cytokines like IL-1β, IL-6, and TNF-α and thus inhibit inflammation, oxidative stress, and apoptosis.

7. DISCUSSION

Unhealthy or improper food consumption can cause obesity, diabetes, hyperlipidemia, high blood pressure, gall bladder diseases, and even cancers (161). Obesity or an increase in weight gain accelerates damage to weight-bearing joints, which causes chronic joint pain and degeneration (162). In obesity, the excessive free fatty acids deposit in major organs such as in the arteries, causing atherosclerosis, and in hepatocytes, causing NAFLD (161). Many the over counter medicines and prescription drugs have been used for preventing possible hazards associated with obesity and also for prevention and treatment of inflammatory disorders. These including NSAIDs which are frequently prescribed by doctors for various musculoskeletal disorders to relieve pain and inflammation however, their hepatotoxicity is a major health concern sine liver is the main site of their metabolism. Their side effects vary from asymptomatic elevations in ALT/AST levels and fatty infiltration of the liver to hepatitis with jaundice and even liver failure (163). Therefore, the improved alternative therapies for this purpose are urgently required. Melatonin seems as a candidate as it is safe with little side effects and it has the potent anti-inflammatory activity. Since the chronic inflammations plays a key role behind the etiology of other chronic diseases melatonin may emerge as a supportive treatment against inflammatory disorders (164). Melatonin has a significant role in the regulation of circadian rhythm, and this makes melatonin useful for treatment of various circadian disrupted diseases like sleep disorders, cardiovascular and neurodegenerative diseases (102). At molecular level, melatonin inhibits NF-κB from translocating to the nucleus to bind onto DNA. This prevents the upregulation of inflammatory cytokine transcription and translation, such as that of interleukin (IL)-1, IL-6, and TNFα. Additionally, expression of 5-lipoxygenase, a crucial component in the activation of inflammation, is also downregulated by melatonin (164). The results from study on night shift workers indicate that circadian desynchronization causes metabolic syndrome with dyslipidemia, hyperglycemia, altered hormonal levels and increased proinflammatory markers (165) which can be reduced by melatonin. Many actions of melatonin are receptor-independent including scavenging free radicals and interacting with cytosolic proteins (tubulin-associated proteins and calmodulin). Some actions are mediated by specific nuclear or membrane receptors (166, 167). Chronic inflammations cause pathological changes in various signaling pathways which automatically uplift the levels of ROS/RNS resulting in oxidative stress. Oxidative stress can be abated by melatonin (102). Melatonin can detoxify ROS/RNS through several processes, including radical adduct formation, hydrogen transfer, single electron transfer, inhibition of pro-oxidant enzymes, reducing free radical generation, and thus boosting mitochondrial function (102). As the circadian clock governs lipid metabolism, the gut microbiome distribution and energy metabolism, the disruption of circadian rhythm can raise the risk of obesity, which may ultimately worsen circadian turmoil with its negative consequences (168). Melatonin is considered as the important component of circadian rhythm. In Zucker diabetic fatty rats, which is an experimental model for circadian disruption, metabolic syndrome and diabetes *mellitus*, melatonin lowered their fasting glucose level, improved their insulin sensitivity and function of β cells of pancreas. Besides, melatonin's anti-inflammatory activity yields positive effects against chronic inflammation that is the root cause of many chronic diseases, it can also emerge as a new pharmacologic agent against obesity related diabetes for maintaining glucose homeostasis (169).

8. CONCLUSION AND FUTURE PERSPECTIVES

Obesity and its associated disorders, particularly NAFLDs have greatly increased worldwide, and the use of NSAIDs has also increased accordingly which can cause serious

side effects. The need to identify the novel anti-inflammatory medicines with fewer side effects is urgently required. From the above discussion, it can be affirmed that melatonin has remedial effects on hepatic damage induced by both NSAIDs and obesity. Melatonin is a versatile molecule with positive effects; it can emerge as a potent therapeutic compound against different disorders involving obesity and inflammation and can reduce the side effects of many NSAIDs.

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AUTHORSHIP

DB conceptualized, critically revised, and approved the manuscript. AN developed, wrote, and revised the concept. SG revised and edited the manuscript. TD edited the manuscript. AC critically read, revised and approved the manuscript.

CONFLICT OF INTEREST

There is no conflict of interest.

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