A Review of Biological and Pharmacological Actions of Melatonin: Oxidant and Prooxidant Properties

Melatonin as an indoleamine exists in most of mammals and produced by various organs. It involved in circadian regulation of physiological and neuroendocrine function. Also it modulates diverse physiological functions such as sleep and sexual behavior. During the last decade, melatonin has been shown to possess potent free radical scavenger properties against reactive oxygen species (ROS). Moreover, by induction of the expression of antioxidant enzymes and reduction of the activation of pro-oxidant enzymes, melatonin indirectly could protect cells against a variety of free radical-related diseases. Besides, melatonin has been shown to promote the generation of ROS at pharmacological concentrations in in-vitro studies. Although melatonin could potentially be useful but safety, efficacy remains uncertain. In the present report, we review the studies which document the influence of melatonin on the various oxidative stress associated diseases .We also analyze the possible mechanisms by which melatonin induce ROS formation.

Keywords: melatonin • antioxidant • anti-inflammatory • pro-oxidant • oxidative stress • free radicals

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Introduction

Melatonin (N-acetyl-5-methoxytryptamine), an endogenous neurohormone, is an evolutionary conserved indolamine synthesized from tryptophan that is the mainly secreted by the pineal gland [1]. Extensive effects of melatonin and its metabolites are associated to their physiological functions such as regulating sleep(circadian rhythms) as time-giver (Zeitgeber) [2], alleviation of depression [3], synchronizing the reproductive cycle with the suitable period of the year in photoperiodic species [4], anti-aging [5], antioxidant [6], anti-inflammatory activities [7,8] and newly recognized pro-oxidative effects [9] in exogenous administration. Secondary sources of melatonin are retina, gut, platelets, skin, bone marrow and other organs, which have minor systemic roles [4]. Also melatonin can modulate a variety of neural, endocrine, and immune functions [4].

Reportedly, melatonin has shown potential therapeutic effects in several diseases such as Alzheimer [10], obesity [11], cardiovascular [12], bone disease [13] and cancer [14,15]. Besides, some prior studies have revealed that melatonin can recover colonic damage in experimental colitis [16,17]. ROS formation is a fundamental stimulant of various signaling cascades including cellular proliferation, survival, inflammation and senescent. Because of prominent antioxidant properties melatonin confronts the progression of inflammatory cascades [18].

Melatonin acts both receptor-dependently as well as independent pathways; the latter relate to its direct radical scavenging functions. Melatonin effects are via largely through G protein dependent receptors which result in the stimulation of antioxidant enzyme production against oxygen- and nitrogen-based reactive molecules [19]. Specific membrane and nuclear receptors have been recognized for melatonin in non-neural tissues from many different species [20]. There are melatonin receptors type 1 and type 2 (MT1 and MT2, respectively) or, indirectly with nuclear orphan receptors from the RORa/RZR family. Melatonin also couples to the quinone reductase II enzyme, previously defined the MT3 receptor [21]. Understanding the distribution of peripheral melatonin receptors and their function seem quite remarkable, since melatonin modulates

widespread processes in the whole body including immune-modulation, regulation of endocrine, pulmonary and cardiovascular functions, as well as cancerogenesis, and aging [22]. Some evidence showed that melatonin supplementation during the phase of diabetes development protected the liver against oxidative stress and the consequences of DNA damage [23].

The present review focuses on recent insights into the various biological functions of melatonin and bolds the importance of the agent as a valuable pharmacological tool once more.

Melatonin anti-oxidant effects

Owning an amphiphilic nature, melatonin easily enters the entire cell compartments such as nucleus [24] and mitochondria where it scavenges free radicals [25,26] and directly inhibits mitochondrial permeability transition pore (MPTP) [27]. Also, melatonin is able to prevent molecular damages resulting from toxic oxygen- and nitrogen-based reactants [28-30]. Melatonin functions in scavenging free radicals might be classified in to four main categories (Figure1): (1) as an antioxidant directly scavenges ROS [31], (2) stimulates the antioxidant enzymes production and activation [32,33] and (3) increases the efficacy of mitochondrial functions by improving MPTP, inhibition of cytochrome c release and refining

of oxidative phosphorylation in mitochondrial respiratory chain which further will decrease the peroxidation of membrane lipids [34]. Melatonin inhibits peroxynitrite production and activation of poly ADP ribosesynthetase (nuclear enzyme) in macrophages of rats exposed to zymosan-induced shock [35]. Inhibition of peroxy nitrite production by melatonin cause anti-inflammatoy effects (4) [36]. Recently studies revealed the participation of nitric oxide in the mechanism of anti-inflammatory effect of melatonin [37].

It has been discovered melatonin was more effective than vitamin C in an experimental model of Alzheimer disease [38] and has exerted better protective effect than vitamin E and N-acetyl cysteine against acetaminophen induced oxidative stress toxicity in mice [39].

Melatonin as an anti-oxidant in Liver disease

Due to high amounts of intracellular concentrations of glutathione(GSH), superoxide dismutase (SOD), catalase, and lipid soluble antioxidants [40], hepatocytes are stable to injuries caused by Reactive Oxygen species (ROS) and Reactive nitrogen species (RNS). However, oxidative stress in part, is involved in different liver dysfunctions including fatty liver diseases, drug-induced liver injuries and even alcoholic liver diseases [41-44]. Hence, anti-oxidant therapy in context of counteracting the harmful effects of ROS and therefore preventing
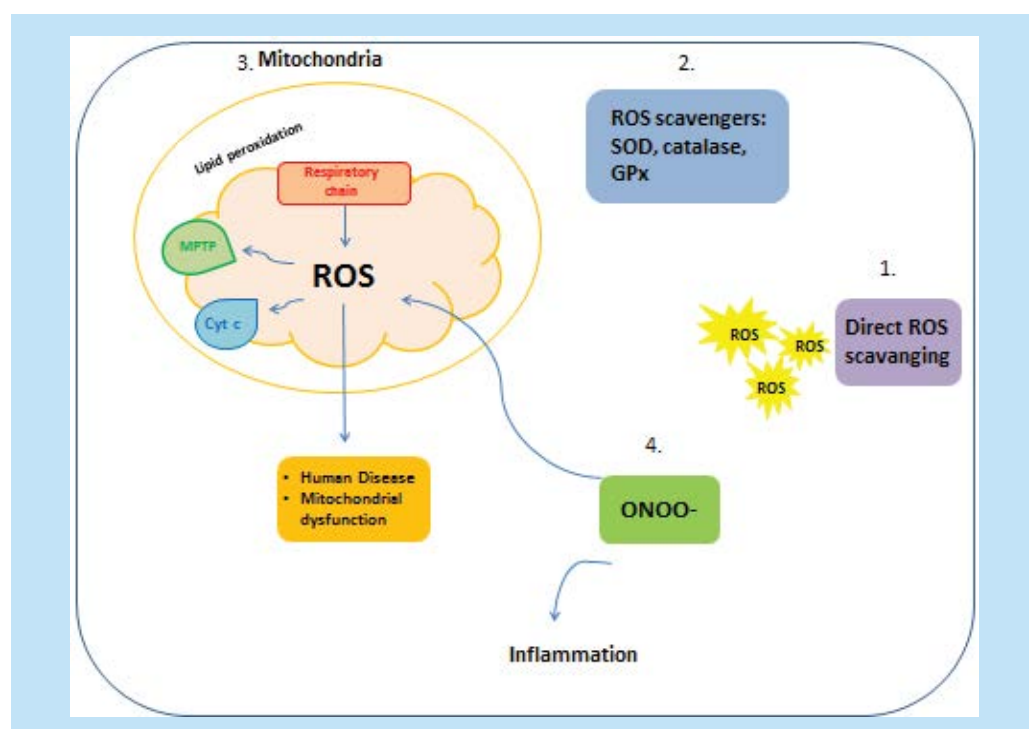

Figure 1: Four points of melatonin effect as an antioxidant.

or treating oxidative stress-related diseases is a noteworthy therapeutic option.

Melatonin exerts anti-oxidant effects in hepatocytes and epithelium of liver by reducing lipid peroxidation and increasing the level of reduced liver glutathione [44,45]. Melatonin is a highly valuable OH and H2O2 scavenger, during its metabolism to N-acetyl-N2-formyl-5-methoxykynuramine (AFMK) [46].

It also stimulates several antioxidative enzymes such as glutathione peroxidase, glutathione reductase, SOD, and boosts the synthesis of GSH .The antioxidant properties of melatonin prevent acute liver injury induced by CCl4, acetaminophen, ischemia-reperfusion, bile duct ligation, pancreatitis nephrotoxicity and neuronal degeneration [47-56]. Also, administration of melatonin exerts hepatoprotective effects in a rat model of CPB(cardiopulmonary bypass model) and SIRS(systemic inflammatory response syndrome) by reducing the ROS generation which is well demonstrated in biochemical and histo-pathological experiments [57,58].

As Sewerynek et al has been reported, melatonin increased GSH-Px (Glutathione peroxidase) activity and at the same time reduced free radical injury to the brain and liver of rats treated with lipopolysaccharide (LPS) [59]. Administration of 4 mg/kg melatonin LPS-treated rats enhances GSH above basal levels and lowers GSSG concentrations while it has stimulatory effect on GSH-Px. One week administration of 10 mg/kg of melatonin significantly increases SOD activity in rat hepatocytes [60], while some reports show enhancement of SOD activity in rat kidney, liver and brain after a single melatonin injection (5 mg/kg) [61]. This indicates that melatonin may act on several points in the antioxidant defense system, not exclusively on GSH-Px40, which is also evident in drug induced liver injuries. Daily 3 mg/kg melatonin is expected to provide significant protection against acute and chronic liver injuries induced by thioacetamide [62,63]. However, the hepatoprotective activity of melatonin in chronic liver injuries is more favorable of acute liver injuries [64]. Besides, treatment of isolated hepatocytes with melatonin (1mM) reduces the trazodone-induced ROS formation and protects mitochondria against trazodone-induced toxicity [65]. Taziki et al reported that 1mM of melatonin is the effective dose that provides proper protection against trazodone [65]. Simultaneous administration of taurine and melatonin prevented mitochondrial damage caused by phenytoin, and its consequences such

as LPO [66]. Furthermore, 1 mM of melatonin remarkably increased glutathione contents of carbamazepine-exposed cells and decreased the GSSG levels, reactive oxygen species and TBARS production. Incubation of hepatocytes with the 1mM of melatonin decreases the death rate of hepatocytes drastically [67].

Comparison of melatonin with other known anti-oxidant agents has been investigated in some researches. Melatonin, in combination with vitamin C was also vastly efficient in reducing the lipid peroxidation in hepatic homogenates treated with 15 ml FeSO4 and100 ml H2O2 [68]. Vitamin E was found to be approximately 100-times more efficient than melatonin in reducing lipid deterioration under the experimental conditions used [68]. So this is consistent with other observations wherein, under in-vitro conditions, vitamin E was more effective than melatonin in inhibiting the oxidative breakdown of lipids [69].

Melatonin (100 nM) markedly increases the activity of the GPx liver mitochondria by eightfold, compared with the basal levels of these enzymes while, Neither NAC, ascorbate, nor Trolox are able to modify the activity of the glutathione-related enzymes. Besides, melatonin but not vitamins C and E preserves glutathione homeostasis in t-butyl hydroperoxide-induced mitochondrial oxidative stress [70].

Melatonin as an anti-oxidant in pulmonary disease

Oxidative stress is a key pathophysiological reason of airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), which cause significant morbidity and mortality. ROS formation not only causes direct harm to lung structure but also exacerbates other situations such as COPD, inflammatory lung disease and increasing of the epithelial and endothelial cells of the lung apoptosis [71,72]. Oxidative stress stimulates the activation of transcription factors and signaling pathways, partly through the activation of the innate immune response which turns on several cell signaling cascades that leads to release of cytokines and chemokines [73]. It is well known that, chronic oxidative damage in COPD terminates in increased levels of highly reactive carbonyls which could be modified and become a highly immunogenic carbonyl adducts on "self" proteins [74].

A clinical study based on measuring exhaled breath condensate (EBC) collection was organized on which malondialdehyde (MDA) was found to be increased in subjects with

chronic airway disorders, particularly in COPD [75].

Life style habits also result in oxidative phenomena, as in chronically cigarette smoke exposed guinea pigs the oxidative damage to muscle proteins, which precedes the characteristic respiratory changes, may contribute to muscle loss and dysfunction in smokers and patients with COPD [76].

Numerous evidences from clinical trials have presented that exogenous melatonin has positive effects in avoidance of cell damage in acute circumstances, such as sepsis, asphyxia and also chronic metabolic disease, inflammation, and lung cancer [77-79]. Recent reports showed that the production of ROS and pro-inflammatory cytokines are extensively diminished by the treatment with melatonin, thereby melatonin may limit pulmonary injury through its antioxidant properties [80]. Pignone et al described a decreased serum melatonin and antioxidant enzymes activity in erythrocytes together with proof of increased lipid peroxidation during exacerbations in COPD and asthma [81]. There is helpful data that oxidative stress and related compounds can selectively trigger nociceptive airway afferents in bronco-pulmonary airways, initiating action potentials in unmyelinated C-fibers that conduct centrally to inducing dyspnea [82]. TNF-α production was inhibited upon pretreatment with melatonin and IL-10 releasing was increased with the result of decreased pulmonary edema [83]. Also pretreatment of rats with melatonin attenuated malondialdehyde levels in endotoxemia-induced and ventilator-induced lung injuries [84] peritonitis-induced septic shock [85], ionizing radiation induced oxidative organ damage [86] and bleomycin induced lung injury [80]. All of these reports signifying the inhibitory role of melatonin in neutrophil infiltration and lipid peroxidation [83]. It has been published that 8-isoprostane as a Markers of oxidative stress were increased in bronco-alveolar lavage fluid from patients with sarcoidosis [87-89]. Therefore melatonin is a harmless and efficient treatment for CS (chronic pulmonary sarcoidosis) unresponsive to other treatments or when the typical remedy should be stop for dangerous side effects [90].

Melatonin as an anti-oxidant in cancer therapy

Oxidative stress appears to play an essential role in a wide range of cancers due to its association to a variety signaling pathways, apoptosis, survival, and proliferation. The stimulatory function of ROS on transcription factors such as NF-κB, AP-1, p53, HIF-1α, PPAR-γ leads to expression of different genes, including those for growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules [91]. Besides, oxidative hazard provides the situation for chronic inflammation that is a common etiology of several diseases as well as cancer [92]. Cancer cells themselves generate active oxygen and the results by-products that cause cellular damage [93].

Also, polymorphisms in cellular oxidant/ antioxidant reservoirs have been identified in cancer susceptible patients [94]. Hence, antioxidants has been offered as a choice therapeutic option in treatment of malignancies [91,95]. As Lissoni et al works reported, Melatonin is useful in chemotherapy of cancer patient with poor clinical condition [96], advanced cancer patient with normal clinical status [96] and improve the efficacy of anthracyclines, cisplatin, 5fluorourcil, etoposide, gemcitabine, taxanes, raltitrexedand, isofosfamide [96,97].] Melatonin through numerous biological mechanisms is able to influence host–tumor interactions which may change both tumor and host characteristics [98-100]. Melatonin as anti-proliferative [97] and also anti-inflammatory activity [101] happens as a consequence of the inhibitory effect on IL-6 secretion, which prevents anti-tumoral immunity of body [102,103].

Melatonin has been used as a supportive treatment of cancer patients by the prevention of both cancer progression-related symptoms and chemotherapy-induced toxicity [104]. So, melatonin is the first identified natural molecule that may have both therapeutic and alleviating actions in the cure of human neoplasms. Presentational agents are generally limited to endocrine-dependent tumors (breast, endometrial, prostate), whereas, melatonin is potentially effective against most solid tumors (lung, gastric, colorectal) cancer [104,105].

Bartsch et al demonstrated that the level of overnight plasma melatonin decreases due to the changing of 6-sulfatoxymelatonin metabolism and other compounds in the DMBA(Dimethyl benzanthracene) exposed rat livers [106]. So, exogenous melatonin could act as a defensive hormone against DMBA-induced carcinogenesis by effectively repairing of the antioxidant enzyme system (full protection for CAT, SOD and an adequate protection for GSH Px) [107]. Furthermore, melatonin suppresses iron related carcinogenesis by inhibiting of lipid peroxidation

and sperm abnormalities in male gonads [108-110]. Also melatonin shows higher efficacy than combination of vitamin E/ Se in antagonizing ROS effects [107].

Oxidative damage initiated by AFB1(aflatoxinB1) may be one of the underlining mechanisms for AFB1-induced cell and DNA damage, which ultimately lead to tumorigenesis [111]. Also AFB1 can trigger caspase-3 activation and lead to apoptosis in rat liver [112] and in vivo studies suggest that AFB1can cause lipid peroxidation in rat liver [113]. Melatonin treatment improve hepatic antioxidant defense system which consequently decrease the apoptosis rate in the liver [114] and according to all the previous evidences and results of some clinical studies melatonin can be used as a treatment in clinical cases of aflatoxicosis [112,115].

Melatonin as an anti-oxidant in Cardio-vascular disease

There are many biological factors such as hyper-cholesterolemia, diabetes, infectious agents and an excess of free radicals could cause cardiovascular disease. According to many studies reactive oxygen species play key role in pathogenesis of coronary atherosclerosis [116-118]. Moreover, ROS and subsequently oxidative stress been recognized in the development and maintenance of hypertension has for some time [119-121]. The accumulating data from several experiments suggest that melatonin influences the cardiovascular system [122-124].

Melatonin could effect on circulatory function via different mechanisms. For example melatonin can maintain the availability of nitric oxide, so lead to vasodilatation and reducing blood pressure [125]. Also, melatonin has an inhibitory effect on α1-adrenergic and also increase the cholinergic tone [126]. Oxidative stress is highly involved in endothelial dysfunction and is a denominator of vascular disease. Decrease in synthesis or elevated inactivation of NO is a predictive of future cardiovascular events.

Accelerated ROS generation reduces the amount of bioactive NO by chemical inactivation to form toxic peroxynitrite [127]. So, Melatonin via acting as an antioxidant may in part improve endothelial function.

Ekmekcioglu et al suggest that recently founded MT1 and MT2 melatonin receptors in some parts of human cardiovascular system such as left ventricle, aorta, and coronary, cerebral illustrate the distinguishing role of melatonin in treatment of cardiovascular disease such as hypertension,

myocardial ischemia, and stroke [128].

Some clinical studied have shown that daily administration of 1mg melatonin could reduce systolic/diastolic pressures and norepinephrine levels in young women and men [129,130]. As well, other study proved that repeated dose of oral melatonin intake 1 hour before bedtime reduced blood pressure and also enhanced sleep quality in male patients with essential hypertension [131].

In contrast to the beneficial effects of melatonin, Lusardi et al works showed that, co-administration of melatonin and nifedipine increased blood pressure heart rate in hypertensive patients [132]. These findings suggest that that melatonin may compete with nifedipine and diminish the antihypertensive effect of the calcium channel blockers, so melatonin cannot be considered a dietary supplement [132]. Besides, clinical evidences has been shown that melatonin in combination with antihypertensive drugs treatment, increased the effect of aforementioned drugs [133].

Several studies have investigated the antioxidant effect of melatonin on total cholesterol and VLDL (very low-density lipoprotein). Tengattini et al reported that plasma levels of total cholesterol and very low-density lipoprotein cholesterol as well as the low-density lipoprotein cholesterol sub-fraction was reduced by melatonin in hyper-cholesterolemic rats [134].

Melatonin may demonstrate the effects by enhancing endogenous cholesterol clearance. Since, melatonin has a lipophilic property, it can enter the lipid phase of the LDL particles and inhibit lipid peroxidation [135]. Also melatonin by increasing of endothelial NO production can protect human umbilical artery against the oxidation of low-density lipoprotein [136], consequently it would be protective against cardiovascular disease [134].

Pro-oxidant effect of melatonin

The pineal indolamine, melatonin, in addition to acting as a well-established antioxidant it also has been reported recently to exert pro-oxidant activities. Increased formation of ROS or decreased cellular antioxidant reservoir called oxidative stress results in cellular damage by oxidizing the macromolecules such as proteins, lipids and DNA [91]. Various cell functions including signal transduction pathways, host defense against invasive pathogens, autophagy, cellular proliferation and apoptosis are mediated by physiological amounts of ROS [137]. Besides ROS is produced in response to different

cytokines and growth factors as a secondary messenger [138,139].

Although the imbalance between oxidant/antioxidant particles increases ROS levels resulting in undesirable effects, ROS mediated apoptosis in a wide spectrum of cancers is the mechanism by which many chemotherapeutic agents induce cytotoxicity [140].

Melatonin by scavenging free radicals and activating of intracellular antioxidant enzymes acts as a powerful antioxidant [141]. In addition to having role in cell signaling pathways, melatonin protects normal cells against apoptosis [142,143]. Controversially, melatonin induces programmed cell death in several cancer cells as in human myeloid HL-60 cells [144], human colorectal cancer cell [145], human prostate adenocarcinoma cells [146] and B-lymphoma [147]. While the exact mechanism of melatonin induced apoptosis remains to be elucidated, its pro-oxidant activity, presumably, constitutes a mechanism that may result in tumor cell death by apoptosis. ROS induced apoptotic pathways enables melatonin to reduce cell proliferation rate in different cell types [148]. Enhancement of intracellular ROS production was observed after melatonin treatment in human pro-mylocytic leukemia HL-60 cells 9. Increase of intracellular ROS generation exacerbates intrinsic pathway of apoptosis which is usually followed by a loss of mitochondrial membrane potential [149]. Disrupting mitochondrial function, melatonin induces the liberation of cytochrome c from mitochondria into the cytosol which in turn activates caspase enzymes cascade. Inhibition of melatonin induced caspase activation by known antioxidants suggests the pro-oxidant effects of melatonin accounting for its cytotoxic role in HL-60 cells [144]. Moreover, Bejarano et al, demonstrated that melatonin provokes hydrogen peroxide induced oxidative damage accompanied by marked intracellular ROS production, mitochondrial dysfunction, reduced metabolic capacity and elevated caspase 9 activation in HL-60 cells [150].

In addition, melatonin potentiates chemotherapeutic –induced apoptotic effects of anticancer agents that generate intracellular ROS [151]. Melatonin is involved in significant depletion of glutathione (GSH), which protects cells against oxidative hazard, causing a pro-oxidant mechanism related to the cytotoxic features of this indolamine. Melatonin reduces GSH level and subsequent overproduction of ROS in human liver cell line HepG2 [152].

Albertini et al, also reported a prooxidant effect of melatonin in U937 cells within the increment of intracellular oxidative species and depletion of GSH while the glutathione peroxidase activation was unchanged during the experiment [153].

Fas ligand is a trans-membrane protein subsequent to binding to its receptor plays a fundamental role in apoptosis induction. Oxidative stress induces the expression of fas receptor and fas ligand. Melatonin pro-oxidant properties triggers fas-induced cell death in human leukemic Jurkat cells [154].

Despite antagonizing deleterious oxidants generated in the cell medium, melatonin itself could be oxidized by the free radicals such as AAHP-derived peroxylnitrit radicals (ROO.) and produce melatonin radical which in turn is able to react with GSH [155].

Influencing cell signaling pathways, but not direct chemical effects of melatonin has also been proposed as the prooxidant mechanism of the substance. In this context, the activation of lypoxygenase(LOX) and phospholipase A2 (PLA2) are assumed to participate in melatonin induced ROS production [156]. Since calmodolin is a low affinity target of melatonin, their binding lead to Ca2+-independent release of PLA2. Upon moving to the cell membrane PLA2 liberates high amounts of arachidonic acid which in turn stimulate LOX activation and subsequent ROS production [157].

To note, affecting cellular redox state and pro-oxidant activities of melatonin are concentration dependent. Such properties have been reported in both high micro-mill molar concentrations of melatonin unlike the physiologic amounts which exert antioxidant and anti-proliferative properties [158]. Taking into the account the dual antioxidant abilities related to the anti-proliferative and pro-oxidant abilities related to the cytotoxic effects of melatonin opens the door to novel indication of the indole in different cancer cells.

Anti-inflammatory Properties of Melatonin

The antioxidant and anti-inflammatory effects of melatonin extensively have been summarized in many studies6,156,159. Malondialdehyde (MDA) and inflammatory cytokines concentration have been reduced after melatonin treatment in critical situations such as asphyxia, sepsis, and surgery [160-162].

The production of inflammatory cytokines

including TNF-α, IL-1β, or IL-6, subsides by melatonin in numerous experimental models of inflammation [163-166]. Different mechanisms have been reported for anti-inflammatory activity of melatonin including prevention of the activation of cyclooxygenase-2 and inducible isoform of nitric oxide synthase, as well as blocking of the transcriptional factors-that stimulates pro-inflammatory cytokines production [167,168]. These include not only NFk-B but also, HIF, Nrf2, cAMP, CREB, STAT, PPARs, and AP-1.

Melatonin exerts anti-inflammatory effects both under in vitro and in vitro conditions. Besides, in an experimental human sepsis model, melatonin administration before endotoxemia results in significant reduction of certain markers of inflammation [169]. The protective effect of the indolamine on acute model of pancreatitis has been investigated. Caerulein-induces acute inflammation in pancreas of rats whereas, melatonin pre-treatment diminishes pro-inflammatory cytokines IL-1β and TNF-α and increases the serum levels of anti-inflammatory cytokine IL-4 170. These results are consistent with the findings about acetic acid-Induced Colitis in rats that melatonin completely improves the latter inflammation [171]. In rabbit osteoarthritis (OA) model and also human chondrocytes melatonin markedly inhibits hydrogen peroxide cytotoxicity via downregulation of iNOS, and COX-2 protein and mRNA expression [172]. Furthermore, melatonin , in a dose dependent manner decreases the iNOS protein expression and TNF-α mRNA levels caused by methamphetamine in human dopaminergic neuroblastoma SH-SY5Y cells . The anti-neuroinflammatory effects of melatonin result from the inhibition of activated NF-κB in cell signaling pathway [173].

Based on mentioned observations, melatonin can be used in combination with other drugs such as omeprazole to treat ulcerative colitis [174,175]. Chen et al have reported that melatonin administration decreases abdominal and rectal pain in patients of irritable bowel syndrome176. Other clinical study demonstrate melatonin plus tryptophan treatment are effective by decreasing the plasma levels of pro-inflammatory cytokines in patients with nonalcoholic steatohepatitis [177]. Surprisingly, a clinical study on patients with rheumatoid arthritis has been revealed the combination of melatonin treatment with other medications did not improve the clinical symptoms and it has been observed concentration of some inflammatory indicators increased [178].

Regarding to decreasing of melatonin level in many infectious patient such as HIV-1 [179], pulmonary tuberculosis [180], melatonin treatment are valuable to use against numerous bacterial and viral infections due to its anti-inflammatory ,antioxidant, immune-modulating actions [181].

Conclusion

A large number of evidences have indicated a tight, cause-effect link between oxidative stress and a broad range of human diseases since it can contribute to many of cell signaling pathways and of course be hazardous in case of excess ROS generation. Hence, use of suitable antioxidant with maximum protection has always been a matter of many experiments. Melatonin due to its known powerful ROS combating properties has attracted many attentions. Definition of the role of melatonin in the patho-physiological mechanisms of inflammation has also been a growing research field. Regarding the pro-oxidant stimulating effects of melatonin clarifying the proper amount and duration of its use should be taken into the account.

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