Review

A comparative overview on the role of melatonin and vitamins as potential antioxidants against oxidative stress induced degenerative infirmities: An emerging concept

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ABSTRACT

Oxidative stress is a biological phenomenon clarified as the decreased ability of the antioxidative system to neutralize the excessive reactive oxygen species (ROS). At a low concentration, ROS serves as a signal molecule to exert its physiological functions but the persistently excessive ROS predisposes a variety of disorders including coronary heart diseases, atherosclerosis, diabetes *mellitus*, hemolytic anemia, pulmonary diseases, neurodegenerative disorders, etc. The use of antioxidants to protect against oxidative damage is a well-established practice. In these aspects, melatonin and other classical antioxidant vitamins such as carotenoids, α-tocopherol, vitamin D, and ascorbic acid have gained enormous research attention currently. In this review, we will discuss the comparative as well as the synergistic actions of melatonin and other antioxidant vitamins in the treatment of oxidative stress-associated disorders. Noteworthy, based on the evidences we will discuss, we recommend the combination of melatonin and vitamins to alleviate oxidative damage in the broad spectrum.

Keywords: ROS, antioxidant, vitamin, melatonin, synergistic action, degenerative diseases.

1. INTRODUCTION

Reactive oxygen species (ROS) or reactive oxygen intermediates (ROI) are produced as the by-products of normal cellular metabolism. At low or moderate concentrations, ROS facilitates several physiological processes including the killing of invading pathogens, wound healing, and tissue repairment (1). ROS also acts as important signaling molecules by modulating several redox-sensitive signaling pathways. A delicate balance exists between ROS production and antioxidant defense capacity in all organisms. This balance maintains the homeostasis of the intracellular environments, otherwise, its imbalance will cause oxidative damage to cells. It has

been documented that oxidative stress perturbs the mitochondrial function of energy supply and leads to apoptosis (2). Naturally, cells are equipped with antioxidant machinery including enzymatic components such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx) (3) as well as non-enzymatic substances including vitamins such as ascorbic acid, alpha-tocopherol, carotenoids and vitamin D (4). Most of these vitamins, except vitamin D, are acquired from the diet. They are highly crucial for maintaining normal cellular functions and their deficiencies may predispose health issues (4).

Melatonin (N-acetyl-5-methoxytryptamine), a tryptophan derivative, is well recognized for its antioxidative function. A combination of free radical scavenging, metal chelating, and antioxidative enzyme stimulating properties make melatonin a superior choice over other classical antioxidative molecules (5). Despite the endocrinal properties of melatonin, it can be portrayed as a vitamin from a nutritional point of view since it is also present in foods including vegetables, fruits, seeds, rice, medicinal herbs, meat, fish, eggs, and wine at high concentrations (6, 7). Melatonin possesses several functional similarities with vitamin D and A (6). Numerous studies have confirmed the antioxidant potency of melatonin and the underlying mechanisms through which melatonin counteracts oxidative stress (8-11). However, to our best knowledge, few studies have investigated the preventive potential of vitamins on oxidative stress-associated diseases. Additionally, synergistic effects of melatonin and vitamins toward amelioration of oxidative damage remain less explored yet. This review aims to discuss the potential role of vitamins and melatonin in attenuating tissue or cellular oxidative damage, either synergistically or additively.

2. ROS PRODUCTION AT A GLANCE

Electron transport chain (ETC), the major energy generating pathway, is the harbor of free radical generation. Leakage of electrons from the respiratory chain generates super-oxide anion ($O_2^{\bullet -}$), which further leads to the formation of highly reactive hydroxyl radical (•OH), lipid peroxides, hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl) along with reactive nitrogen species (RNS) such as nitric oxide (NO) and peroxynitrite (ONOO•) (12, 13). The H_2O_2 is mainly generated by superoxide dismutase (SOD). In the presence of transition metals such as Fe^{2+} and Cu^{+}, H_2O_2 is catalysed to form the most deleterious •OH via Fenton reaction (13-15) (Figure 1). In addition, other enzymatic reactions also can produce ROS including the NADH oxidase, cycloxidase 2 (COX 2), and, cytochrome P450 system (14-17). The phagocytotic process also involves in free radical generation. The non-enzymatic reactions are another source of ROS generation when oxygen reacts with certain organic compounds, cells are exposed to ionizing radiation, or mitochondria are stressed (16-18). Generally, when heavy metals (Cd, Hg, Pb, Fe, and As), some drugs (cyclosporine, tacrolimus, gentamycin, bleomycin), chemical solvents, oxidized food (smoked meat, used oil and fat), cigarette smoke, alcohol are exposed to cells under certain conditions, all of them can produce free radicals as by-products (1, 18, 19). The excessive ROS oxidizes lipid, protein, DNA, and damages cellular structures (14-17). Especially, the •OH and ONOO• are the most reactive species and are the major culprits of cellular lipid peroxidation and membrane damage (2). ROS can also make proteins and DNA oxidative damage to form carboxyl protein and 8-hydroxyguanosine, respectively (2, 20, 21). Overproduction of free radicals for a prolonged period not only triggers chronic and degenerative diseases including atherosclerosis, diabetes, neurodegenerative diseases, arthritis, and cancer but also accelerates the aging process and inflammation (22, 23).

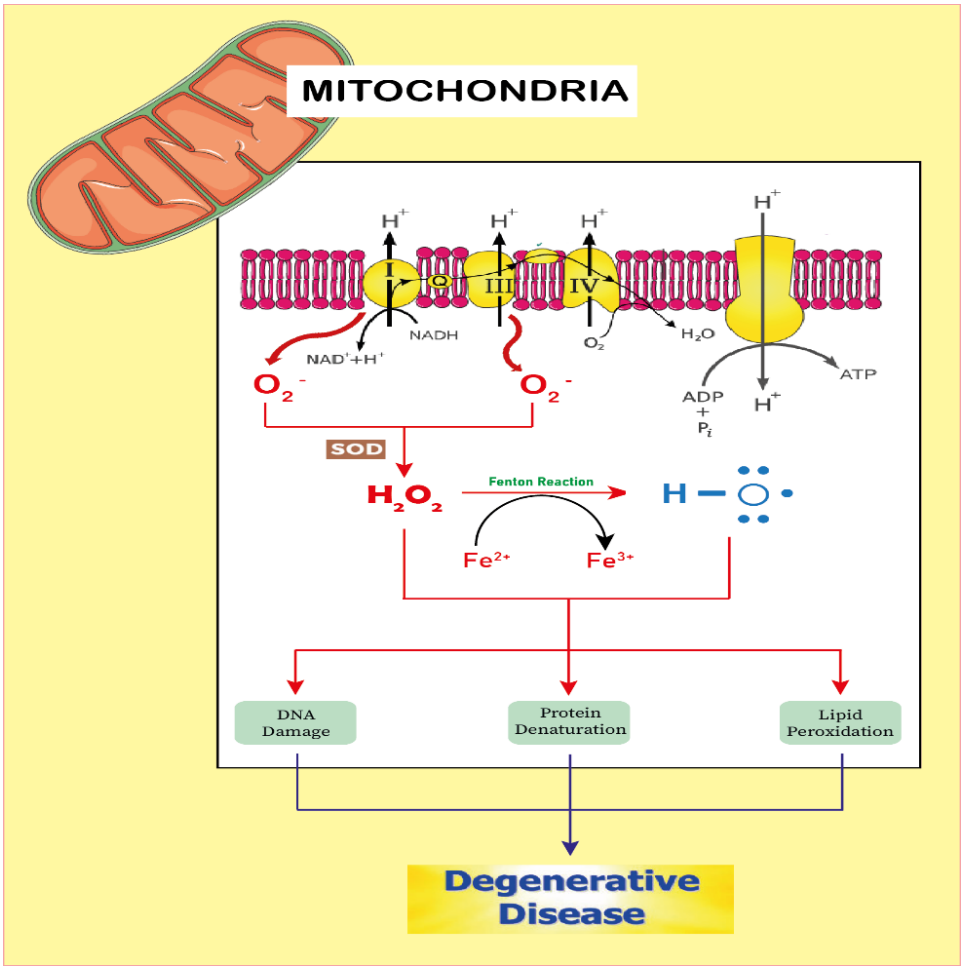

Fig. 1. ROS generation in mitochondria and the potential consequences.

3. ANTIOXIDANTS AGAINST OXIDATIVE STRESS

Antioxidants are those compounds that inhibit molecular oxidation by interrupting radical chain reactions (24). They can donate electron(s) to neutralize ROS (25). They are usually low molecular weight molecules and can reduce free radicals to cease their propagation reaction and protect the vital molecules. Glutathione, ubiquinol, and uric acid are antioxidants produced endogenously by normal metabolism. Together with the antioxidant enzymes SOD, CAT and GPx they build the first line of cellular defense against oxidative stress (25, 26). This defense system controls the ROS at a low level. This low level of ROS serves as the physiological redox signaling and also the stimulator of endogenous antioxidant machinery (27). Mitochondria-targeted antioxidants are considered more potent than others since mitochondria are the main site of ROS generation. To access mitochondria, these antioxidants are required to cross the mitochondrial membrane (28). For example, the triphenylphosphonium cation (TPP+) with a positively charged phosphorous atom surrounded by a lipophilic surface can enter mitochondria with ease. Therefore, ubiquinone moiety of coenzyme Q and vitamin E conjugated with TPP are considered as mitochondrial-targeted antioxidants (29).

4. VITAMINS AS ANTIOXIDANTS

Several vitamins are the most relevant antioxidants present in our diet and they exhibit a variety of physiological roles in human health (30). Vitamins can be obtained from both endogenous and exogenous sources. Certain vitamins are synthesized endogenously under specific conditions, for instance, niacin is a tryptophan-derived molecule in mammals, and vitamin D is converted from 7-dehydrocholesterol in the skin by UV-B radiation (31). Carotenoids, tocopherol, vitamin D, and ascorbic acid are the most well-known conventional antioxidant vitamins and their roles in maintaining cellular redox status are discussed below.

4.1. Carotenoids.

Carotenoids or provitamin A are naturally occurring compounds that are only produced in the plastid of plants and algae, along with some bacteria and fungi (32). Based on the structure, carotenoids are divided into two classes namely carotenes and xanthophylls. Carotenes are further classified into α-carotene, β-carotene, and lycopene whereas oxygen-derived carotenoids are known as xanthophylls (lutein, zeaxanthin) (33, 34). Since carotenoids are highly lipophilic molecules, they can easily pass through biological membranes, thus forestalling the bilayer of the membrane from radical attack (35). They are highly capable of quenching singlet oxygen, superoxide anion, hydroxyl radicals, peroxyl radicals, and nitrogen-derived radicals. Carotenoids display their antioxidant properties through electron transfer, hydrogen abstraction, or addition reaction. This lipophilic antioxidant also protects against membrane lipid peroxidation (36, 37). Apart from their antioxidant properties, carotenoids also facilitate the regulation of the cell cycle, apoptosis, cell differentiation (38), improvement of the immune system (39), and promoting growth factors (40). Lutein, an anti-inflammatory carotenoid, exerts its function by inhibiting NF-κB pathways (41). Kishimoto *et al*. suggest that the antioxidant and anti-inflammatory actions of lutein can suppress coronary artery disease, atherosclerosis, hypertension (42, 43), and cancer (44). Others also confirmed the protective effects of lutein on myocardium injury from oxidative stress and apoptosis (45).

4.2. Vitamin D.

Vitamin D (calciferol) comprises of two major forms, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_2 is mainly obtained from dietary sources while vitamin D_3 is synthesized from 7-dehydrocholesterol in human skin upon exposure to sunlight. After cutaneous synthesis and/or dietary intake, it undergoes an activation process in the liver and kidney forming 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 (calcitriol), respectively (46). This prohormone not only maintains calcium homeostasis but is also crucial for numerous other physiological activities (47, 48). For example, vitamin D deficiency is prone to developing certain chronic disorders including insulin resistance and type 2 diabetes (49, 50), cardiovascular complications (51), and progressive chronic kidney diseases (52). It acts as a membrane antioxidant by inhibiting lipid peroxidation (53). Sardar *et al*. (54) have suggested that the antioxidant efficacy of vitamin D_3 against lipid peroxidation is similar to that of vitamin E. Vitamin D_3 holds a more prominent influence on the enhancement of the activity of antioxidant enzymes such as glutathione peroxidase (GPx) and glucose-6-phosphate dehydrogenase (G6PDH) than vitamin E (54). Evidence has implied that vitamin D_3 administration in diabetic mice reduces their

ROS formation by down-regulating NADPH oxidase expression (55, 56). Vitamin D improves SOD activity in mice (57-59) and enhances the ROS removal process by increasing the intracellular pool of reduced glutathione via upregulation of glutamate-cysteine ligase (GCL) and glutathione reductase (GR) gene expressions (60). A positive correlation between plasma GSH and vitamin D has been reported by Jain *et al*. (61). Vitamin D_3 exerts its antioxidative action through binding with its nuclear receptor VDR (vitamin D receptor). It regulates intracellular oxidative metabolism by recruiting several nuclear coactivators or corepressors that mediate gene expression. When binding to the receptor, vitamin D_3 induces downstream signaling and controls free radical generation in mice hepatocytes (57, 60, 62).

4.3. Vitamin E.

The antioxidant vitamin was first identified by Evans and Bishop (1922) as a regulatory component of the murine reproductive system (63). It is made up of eight analogs including α, β, γ, δ tocopherols and four corresponding tocotrienols. Among them, the most common form α-tocopherol is present in human tissues (64). It is well documented that vitamin E acts as a potent peroxyl radical scavenger thus it prevents the propagation of chain reaction of polyunsaturated fatty acids in the cell membrane (65, 66). Another crucial role of this vitamin E is to modulate cell signaling pathways. Cell proliferation and differentiation along with apoptosis are efficiently regulated by protein kinase C (PKC). The PKC family have 12 isoenzymes which are expressed in a variety of cells, respectively to transduce cell signaling through receptor activation. It has been reported that PKC is inhibited by α-tocopherol. The plausible mechanism of PKC inhibition lies in the activation of protein phosphatase 2A and increase in PKC- α dephosphorylation (67, 68). Furthermore, vitamin E reduces superoxide anion formation in neutrophils and macrophages and inhibits platelet aggregation and endothelial nitric oxide production (69). Vitamin E deficiency might also induce the risk of heart attack, cancer, stroke, fibrocystic breast disease, epilepsy, diabetes, Parkinson's disease, and Alzheimer's disease (70).

4.4. Vitamin C.

Vitamin C (ascorbic acid) a water-soluble molecule plays a dual role in the redox reaction. Some mammals, other than humans, non-human primates, and guinea pigs, are capable of producing vitamin C from glucose. Humans along with these species have lost gluconolactone oxidase, a key regulatory enzyme for catalyzing the final step of vitamin C biosynthesis, during evolution (71, 72). Vitamin C is a potent reductive agent which is able to donate electrons to neutralize ROS. When ascorbic acid donates one electron, it is transformed into a semi-dehydroascorbic acid or ascorbyl radical. This intermediate is transient and quickly converted into dehydroascorbic acid by losing another electron (73-75). Vitamin C is highly effective to scavenge H_2O_2, •OH, $O_2^{-\bullet}$, and singlet oxygen ($^1O_2$). This property makes vitamin C an important antioxidant to protect cellular components from oxidative damage. Vitamin C also preserves the antioxidant capacity of vitamin E by reducing tocopheroxyl radicals and protects the cell membrane and other cellular compartments (76). However, vitamin C displays a prooxidant effect via promoting the reduction of redox-active transition metals like Fe^{3+} to Fe^{2+} and Cu^{2+} to Cu^{+}, which in turn can reduce H_2O_2, thus, producing the most dangerous •OH through the Fenton reaction. In the human body, the elimination of free iron via the iron-binding protein transferrin and ferritin is a possible approach to targetting vitamin C-mediated oxidation (77).

5. MELATONIN AS AN ANTIOXIDANT

Melatonin is a potent antioxidant due to its ability to initiate a cascade of reactions against free radicals. Melatonin can directly scavenge free radicals (78) while its secondary and tertiary metabolites can also detoxify free radicals. Due to this cascade reactions, one melatonin molecule can quench up to 10 ROS. This characteristic of melatonin is different from other classical antioxidants which can only scavenge a reactive oxygen moiety per molecule. Melatonin is a amphiphilic molecule and can easily pass through the biological membrane to exert its antioxidative effect (79-81). Several comparative studies of melatonin with other endogenous or exogenous antioxidants including vitamin C, vitamin E, NADH, and glutathione in both *in vitro* and *in vivo* conditions have confirmed superiority of melatonin over them (82). Melatonin's metabolites such as cyclic-3-hydroxymelatonin (C_3HOM) (83) and *N*-acetyl-5-methoxykynuramine (AMK) (84) are even more efficient hydroxyl radical scavengers than melatonin itself. N^1-acetyl-N^2- formyl-5-methoxykynuramine (AFMK), another metabolite of melatonin, is also capable of quenching radicals through three different mechanisms; (a) radical adduct formation, (b) hydrogen transfer, and (c) single electron transfer (84). In addition, melatonin can stimulates gene expression and activity of several antioxidant enzymes including SOD, GPx and CAT (85) to produce its indirect antioxidant capacity. Therefore, melatonin effectively preserve cell membrane fluidity and function by preventing lipid peroxidation and protein degradation (86).

6. MELATONIN: A STRONG DEFENDER OF MITOCHONDRIA

Mitochondria serve multiple important functions including regulation of cellular metabolism, ATP production and apoptosis. Excess of ROS and RNS production during mitochondrial respiration can lead to cell death. The role of melatonin as a mitochondrial protector was first reported by Mansouri *et al*. (87). When compared to two synthetic mitochondria-targeted antioxidants, MitoQ and MitoE (88, 89) melatonin exhibits similar or even better mitochondrial protective effects than them (90). The implication of these findings supports the fact that melatonin should be considered as an endogenous mitochondria-targeted antioxidant consistent with the proposal that mitochondria might be the intracellular site of melatonin production (91). Many studies have elucidated the ameliorative role of melatonin against mitochondrial injury caused by several threats like ischemia/reperfusion (92, 93), sepsis (94, 95), *in vitro* fertilization (96, 97), β-amyloid peptide (98, 99), arsenite (100) and lipopolysaccharide (101). Additionally, melatonin administration significantly delays the onset and mortality of animal model of Huntington's disease (HD) which is an autosomal neurodegenerative disorder where mitochondrial alteration plays an integral role in the pathogenesis (102). Multiple sclerosis, the most common inflammatory disease of the locomotic neurons with mitochondrial abnormalities, can be alleviated through restoring mitochondrial function followed by melatonin administration (103). Melatonin also preserves the mitochondrial membrane potential which is important for ATP generation and establishing homeostasis in the overall mitochondrial function (104, 105). It stimulates anti-apoptotic mitochondrial protein while suppressing the pro-apoptotic protein expression thus preventing mitochondria associated apoptosis (106, 107). Furthermore, melatonin is also involved in the inhibition of caspase 3 activity as well as the release of cytochrome C from mitochondria (108, 109). Hence, melatonin provides overall protection to mitochondria thus reducing oxidative damage.

7. CUMULATIVE ACTIONS OF VITAMINS AND MELATONIN

Melatonin and other classical antioxidant vitamins have profound effects on cellular redox metabolism. Some of their synergistic as well as combined functions on various organs are discussed below (Figure 2).

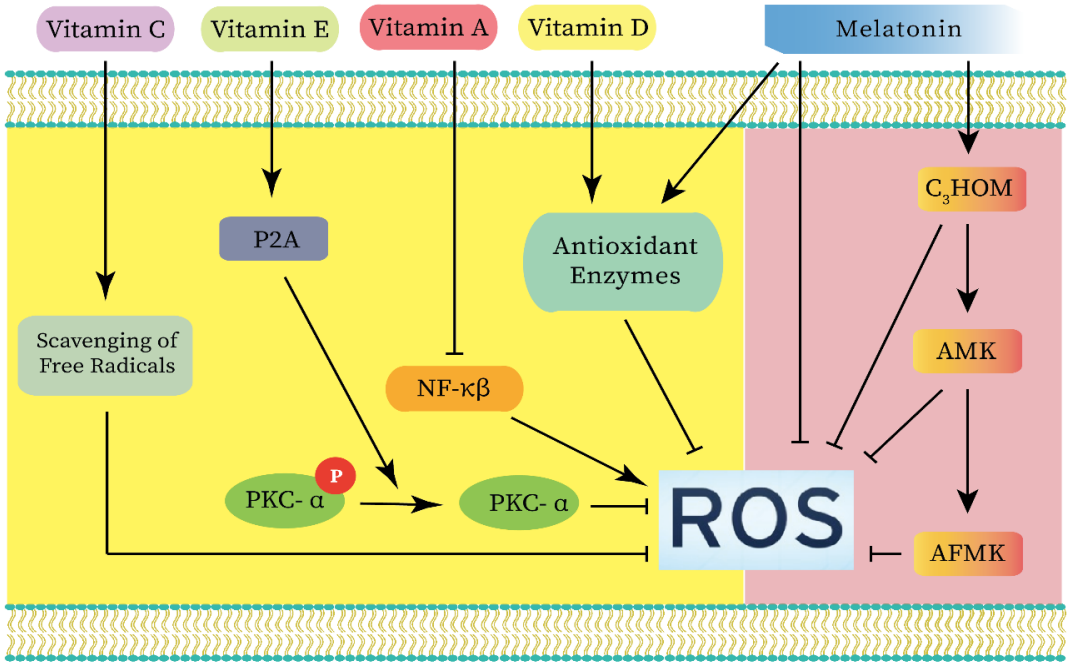

Fig. 2. The action pathways of vitamins and melatonin in amelioration of ROS.

ROS: Reactive oxygen species, P2A: Protein phosphatase 2A, PKC-α: Protein kinase C-α, NF-κβ: Nuclear factor-kappa B, C_3HOM: Cyclic-3-hydroxy melatonin, AMK:N-acetyl-5-methoxykynuramine, AFMK: N^1-acetyl-N^2- formyl-5-methoxykynuramine

7.1. Cardioprotective action.

Pieces of evidence collected during the last 15 years have shown the crucial effects of melatonin on the cardiovascular system (110, 111). The cardio-protective role of melatonin pertains to its direct free radical scavenging and anti-inflammatory activities. It inhibits the release of inflammatory cytokines including TNF-α, IL-1β, and IL-6 while increasing anti-inflammatory mediators such as IL-10 thus, promoting the overall anti-inflammatory effect (112). Since dyslipidemia is a major contributory factor to coronary heart disease (CHD), studies have demonstrated that melatonin regulates blood lipid and prevents oxidized LDL formation, both of which preserve cardiomyocytes from oxidative injury (111). Melatonin exhibits beneficial effects on cardiac health via its receptor-mediated action. Melatonin receptors, MT1 and MT2 are both expressed in the cardiovascular system and are responsible for the regulation of the vascular tone. MT1 mediates vasoconstriction while MT2 mediates vascular dilation (113). On the other hand, vitamin E also shows the cardio-protective effects due to its antioxidant and anti-inflammatory actions (114). Vitamin E attenuates myocardial infarction via diminishing ROS generation and

lipid peroxidation. Many studies have suggested the antioxidant and anti-atherogenic properties of vitamin E in the animal model (115-117). Several clinical studies also support the evidence (118,119). Endothelial nitric oxide (NO) generated by the action of nitric oxide synthase is found to regulate the vascular tone and endothelial functions. Cardiomyocytes express NOS that regulates myocardial contractility, heart rate and cardiac oxygen consumption (120). Chronic alcohol consumption is attributed to reduce NO synthesis and decreases the bioactive NO which is ameliorated by both of melatonin and vitamin C which indicates the potential of the synergistic action between melatonin and other classic antioxidants (121).

7.2. Protection of neurodegenerative disorders.

The complexed chemical constituents of membrane and high energy requirement make neurons more vulnerable to oxidative stress. Neuronal loss will negatively affects the behavior and physiological functions of the individuals. Many acute factors including hypoxia, stroke, physical trauma, hypoglycemia, drug neurotoxicity, viruses, and radiation can cause neuronal damage (122). The glutamate excitotoxicity, oxidative injury and mitochondrial malfunction are three major causative factors related to the neuronal loss (123). Glutamate is an important neurotransmitter in CNS which plays a pivotal role in learning and memory formation. Excessive production of glutamate induces neuronal excitatory effects through activation of glutamate-N-methyl-D-aspartate (NMDA) receptor leading to Ca^{2+} overload and cell death. Amyloid-β protein, a biomarker of Alzheimer's disease (AD), is also a stimulator of glutamate accumulation and an activator of NMDA receptor . NMDA receptor activation further promotes phosphorylation of tau protein and leads to the disintegration of microtubules, loss of synapse and gradually neuronal death (124). Additionally, increased prostaglandin secretion and free radical formation in microglia trigger cytokine production including IL-6, IL-1β, TNF-α that contribute to neuronal damage (125). It is well known that mitochondria play a pivotal role in energy metabolism and apoptosis in brain cells (126). Mitochondrial dysfunction results in decreased ATP formation and ROS generation leading to apoptosis (127). Impaired mitochondrial proteins related to electron transport chain are associated with pathophysiology of AD, Parkinson's disease (PD), and amylotrophic lateral sclerosis (ALS) (128, 129). Melatonin is considered as a neuroprotective agent as it shows anti excitatory and sedative effects (130-132). The protective mechanism of melatonin is partially mediated by the GABAergic system indicating that melatonin inhibits the β-amyloid peptide toxicity through the activation of GABA receptors (133). Melatonin also can promote gene transcription of antioxidant enzymes of SOD-1, CAT and GPx in the cortex of transgenic AD mice (134). Melatonin controls ROS production by inhibiting NADPH oxidase which is the main source of oxidative stress in AD brain (135). Furthermore, the protective action of this ubiquitous indole against AD and PD may contribute to its role in maintaining mitochondrial homeostasis (136). Moreover, vitamin E is also a neuroprotective agent. For example, vitamin E deficiency is mostly related to neurological complications (137-139). Many other studies have demonstrated that α-tocopherol protects neurons from oxidative stress in both the *in vivo* and *in vitro* conditions (140-142). The anti-inflammatory as well as antioxidative actions of this vitamin are attributed to its neuroprotective function. It has been found that α-tocopherol supplementation can reduce the synthesis of inflammatory mediator prostaglandin E2 by inhibiting the activity of cyclooxygenase 2 (COX-2) (143). Furthermore, vitamin E inhibits p38 MAPK (mitogen-activated protein kinase) thus, hindering phosphorylation of tau protein since phosphorylated aggregation of tau causes neurofibrillary tangles which is an important biomarker

in AD brain (144). Montilla Lopez P *et al*. (145) have demonstrated that the toxicity of ocadeic acid in neuroblastoma cells is mitigated by administration of both melatonin and vitamin C. However, melatonin is more efficacious than vitamin C. (Table 1).

Table 1: Comparative studies of melatonin and vitamins.

Investigator	Main findings and conclusion
Montilla P *et al*. (2001) (182)	In rat cholestasis model, melatonin and Vitamin E both reduce the oxidative biomarkers (MDA, GSH) and increase the activities of antioxidant enzymes (CAT, SOD, GR), but melatonin at a dose of 500µg/kg body weight (b.w) is more efficient than that of vitamin E at 15mg/kg b.w.
Montilla-Lopez P *et al*. (2002) (145)	A dose dependent study of melatonin and vitamin C against okadaic acid induced oxidative stress in neuroblastoma cells show that both can significantly reduce oxidative damage. However, vitamin C could not restore GPx, GR and CAT activities. Melatonin exhibits better protection by declining lipid peroxide level more than vitamin C.
Karaoz E *et al*. (2002) (183)	Combination of vitamin C, vitamin E, and melatonin significantly lowered MDA production in lungs of male Wister rats followed by chlorpyrifos ethyl (CE) treatment. Endogenous antioxidant enzymes (SOD, GPx, CAT) levels are more improved in vitamin C+vitamin E and melatonin group compared to CE group. However, SOD activity was found to be more increased in melatonin treated group than vitamin E+vitamin C group. The study suggests that melatonin, and vitamin C plus vitamin E considerably attenuate CE toxicity in lung tissues.
El-Sokkary GH *et al*. (2008) (184)	Melatonin is more potent than vitamin C in regulation of rat hepatic cell proliferation, DNA synthesis and reduction of lipid peroxidation whereas vitamin C is better than melatonin in stimulating GSH level and SOD activity in diazepam induced oxidative stress and hepatocytes proliferation in male Sprague-Dawley rats.
Akinci A *et al*. (2013) (185)	Melatonin provides protection against intensive stress induced gastric damage to a greater extent than vitamin C and β carotene.
Ajibade TO *et al*. (2017) (181)	Melatonin and vitamin C both ameliorate phenyl hydrazine induced haemolytic anaemia and oxidative stress mediated cardiac and renal dysfunction. However, the cardiac, renal and erythrocytes MDA content caused by phenyl hydrazine, was significantly reduced by melatonin and vitamin C with more efficiency in melatonin treatment. The antioxidant enzymes and reduced glutathione content were increased in melatonin as well as vitamin C treated group.

7.3. Prevention of diabetes *mellitus*.

Since oxidative stress is a major factor in the pathogenesis of diabetes *mellitus*; antioxidant therapy could be a suitable strategy to alleviate the symptoms. Being a potent antioxidant, melatonin reduces lipid peroxidation and enhances GPx activity in Type 1 diabetic rats in comparable to vitamin E (146). Melatonin administration maintains normal blood glucose level

and preserves the healthy pancreatic β-cells to prevent insulin leakage in diabetic animal model (147, 148). This indicates melatonin's role in glucose metabolism. Elevated glucose level has been observed in pinealectomized rats even in the presence of high insulin levels. This is probably due to the increased gluconeogenesis in these rats (149). The potential mechanism is that melatonin inhibits phosphoenolpyruvate carboxykinase (PEPCK), the major enzyme in the gluconeogenic pathway, by up-regulating the rate of AKT phosphorylation, required for lowering PEPCK gene expression (149). In addition, melatonin also promotes glucose utilization via the pentose phosphate pathway by increasing glucose-6-phosphate dehydrogenase activity hence, restricting glucose accumulation as well as enhancing NADPH formation required for glutathione metabolism (150, 151). Furthermore, the strong anti-inflammatory action of melatonin confers it more powerful against inflammation-induced metabolic disorders. The inflammation induced by pro-inflammatory cytokines including TNF-α, IL-6, IL-1β, and CRP (C reactive Protein) is a important risk factor of both type 1 and type 2 diabetes (152). In this context, melatonin modulates the pro-inflammatory transcriptional factor NFκB signaling pathway and deactivates NLRP3 (153,154). In diabetic rats, melatonin was found to restore the activity of pancreatic β-cells by improving anti-inflammatory cytokine IL10 level along with lowering the pro-inflammatory cytokines (155). As to other classic antioxidants, since oxidative stress-induced cardiac dysfunction is directly linked to diabetes, thus, vitamin C has been used in diabetic patients in preventing microangiopathy (156), decreasing atherosclerotic plaque and strengthening the vascular integrity (157). An elevated plasma level of vitamin E was observed in diabetes. This could be either the outcome of defective utilization or a compensatory effect to combat stress-mediated diabetes (156). Vitamin D also provides some beneficial effects against diabetes (158). The presence of VDR in pancreatic β-cells indicates its involvement in insulin secretion (158). Vitamin D regulates calbindin, the calcium-binding protein in β-cell which modulates insulin secretion via regulating intracellular calcium (158). An *in vitro* study by Norman *et al*. (159) have showed that insulin secretion is reduced by almost 48% in vitamin D deficient perfused rat pancreas compared with that of vitamin D replenished group The *in vivo* experiments also support the same evidence (160). This antioxidant vitamin indirectly inhibits cytokine-induced pancreatic cell apoptosis via down-regulating NFκB (161). Based on evidences mentioned above, melatonin and antioxidant vitamins have the capacity to protect against hyperglycemia.

7.4. Protection against hemolytic anemia.

Oxidative stress is a major factor to impact functions of erythrocytes. Thalassemia, is a hereditary haemolytic anaemia with absent or reduced production of either α globin chain (α-thalassemia) or β globin chain (β-thalassemia). Both these types are characterized by abnormal erythropoiesis and short red blood cells (RBC) life span with associated symptoms of anaemia, hepato-splenomegaly and iron overload in RBC (162). The haemoglobin oxidation and superoxide anion formation in RBC are the other characteristic features in thalassaemic patients (163). Structural deformities of protein binding in RBC cause hemolysis leading to leakage of free iron in circulation. In addition to endogenous iron release in thalassaemic patients, iron overload occurs due to blood transfusion and oral iron intake (164, 165). In contrast to free iron accumulation, iron deficiency also leads to haemolytic anaemia. Decreased rate of RBC formation with subsequent loss of haemoglobin synthesis is the main outcome of iron deficiency anaemia (166). On the other hand, individuals with G6PDH deficient are also subjected to haemolysis. G6PDH is the key enzyme in the hexose monophosphate (HMP) shunt pathway which generates reducing metabolites

like NADPH in RBC. HMP shunt pathway is the sole source of NADPH formation in RBCs as they are devoid of mitochondria (167). NADPH enhances reduced glutathione (GSH) levels when the erythrocytes are subjected to oxidative stress. G6PDH deficiency in X-linked recessive disorder results in NADPH depletion and diminished GSH regeneration (168, 169). The most common clinical consequences in G6PDH deficient subjects are neonatal jaundice and chronic haemolytic anaemia (170). As oxidative stress seems to be a major etiology in haemolytic anaemia, the application of antioxidants appears effective in combating erythrocytic deformities. In this respect, melatonin seems as a suitable choice (171). Allegra *et al*. have tested the protective effects of melatonin on human erythrocytes from MDA-induced oxidative stress and they observed that melatonin inhibits the vitamin E oxidation (172). The protective mechanisms of melatonin are not only confined by its free radical scavenging activity but also the iron-chelating property. Melatonin chelates iron to prevent hydroxyl radical formation and consequent eryptosis (170, 173). Comparably, vitamin C (174) and vitamin E (175) also have a stimulatory role in erythropoiesis. For example, rats with vitamin A deficiency suffer haematological disturbances including losses of haematopoietic tissue in bone marrow, hypochromia, reduced haemoglobin concentration and splenic accumulation of haemosiderin (176, 177). β-carotene and resveratrol have been reported to directly scavenge ROS in human erythrocyte by improving antioxidant enzyme activity (178). Vitamin C as a reducing agent, facilitates iron absorption as well as iron mobilization. The formation of iron-ascorbate chelate is more soluble in the alkaline medium of the intestine and hence increases its absorption rate (179, 180). The combination of vitamin C and melatonin has been used in preventing phenylhydrazine-induced haemolytic anaemia and associated cardiovascular disorders (181).

8. CONCLUDING REMARKS AND FUTURE PERSPECTIVE

Melatonin as a broad-spectrum antioxidant scavenges free radicals under a variety of physiopathological conditions. The cascade reactions of melatonin with its metabolites make it more potent than other classical antioxidant vitamins. Most of the vitamins only have the capacity to scavenge one ROS per molecule, whereas melatonin having the ability to interact with several ROS and RNS due to its metabolites retaining the capability to further detoxify the radical. For this reason, melatonin scavenges multiple times of more toxic ROS than any other classic antioxidants (186). Hence, from this review we conclude that melatonin is superior than other classical antioxidant vitamins as to its protective effect on oxidative tissue damage. Moreover, melatonin can be an option combined with vitamins and this combination can bring more assertive outcomes toward offering protection against oxidative stress in organisms.

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AUTHORSHIP

Prof. DB contributed to the conception, critical correction of the manuscript and finally approved it. MM prepared the first version of manuscript and figures. RM drafted the figures and tables and edited the manuscript. AB has contributed tofinal formatting and editing the manuscript.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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