Jurnal Keperawatan
Volume 14 Nomor S4, Desember 2022
e-ISSN 2549-8118; p-ISSN 2085-1049
http://journal.stikeskendal.ac.id/index.php/Keperawatan

MELATONIN AND TYPE 2 DIABETES MELLITUS: THE ROLE OF MELATONIN ON PATHOPHYSIOLOGY OF THE DISEASE AND POTENTIAL THERAPEUTIC

Ni Putu Dian Prakanita Dewi*, Nadila, Andreas Galih Sidharta Sugiarto, Kelnia Mellenia, Ade Anjalita Santi Dewi
Faculty of Medicine, Universitas Tarumanagara, Jl. Taman S. Parman No.2 Tomang, Grogol petamburan, Jakarta Barat, Jakarta 11440, Indonesia
*npdianprakanitad@gmail.com

ABSTRACT
Diabetes is a global health problem, with the latest data showing a global prevalence of 536,6 million (10,5%) people. The risk factors involved in the pathogenesis of diabetes, especially Type 2 Diabetes Mellitus (T2DM), are also varied, including a combination of risk factors such as age, obesity, sedentary lifestyle, environmental factors, and genetics. On the other hand, the complications associated with T2DM are also quite diverse, including diabetic neuropathy, retinopathy, nephropathy, and cardiovascular disease. Several theories have been proposed to explain the pathogenesis of complications in T2DM, one of which is cell damage due to oxidative stress. Melatonin is a hormone produced by the pineal gland known for its antioxidant properties, which can provide various therapeutic effects and health benefits, including in T2DM patients. Objective to explain further the bioactivity of melatonin, food sources of melatonin, and the role of melatonin in the pathophysiology of diseases related to its therapeutic potential in individuals with T2DM. This literature review selected various related scientific studies published within the last 10 (ten) years. A literature search was conducted through databases, such as PubMed and Science Direct, with the keywords "melatonin", "Type 2 Diabetes Mellitus", "pathophysiology", and "therapeutic potential". Hyperglycemia in T2DM leads to excessive ROS production, which then causes oxidative stress accumulation and insulin resistance induction. Oxidative stress is known to be associated with many other complications of diabetes, such as cardiomyopathy, retinopathy, and diabetic neuropathy. Melatonin has been shown to protect diabetes through various mechanisms, such as increasing antioxidant status, inhibiting the apoptotic pathway, suppressing inflammation, and acting as a neuroprotective agent. Melatonin supplementation can be used as a therapeutic step to improve pathological conditions in patients and reduce the incidence of T2DM complications.

Keywords: melatonin; pathophysiology; therapeutic potential; type 2 diabetes mellitus

INTRODUCTION
Diabetes Mellitus (DM) is a global health problem, with the latest data showing a global prevalence of 536,6 million (10,5%) people in 2021. This is expected to continue to increase to 12,2% or approximately 783,2 million by 2045. Middle-income countries are expected to experience a greater increase in the relative prevalence of around 21,1% compared to high-income (12,2%) and low-income (11,9%) countries between 2021 and 2045 (Sun et al., 2022). Diabetes mellitus (DM) is a group of common metabolic disorders associated with hyperglycemia conditions. Based on the pathogenesis process, DM can be classified into two major groups: Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). Unlike T1DM, which is associated with autoimmunity, T2DM is more commonly associated with insulin deficiency and insulin secretion, which causes a decrease in insulin function in the body (Jameson et al., 2020). The risk factors involved in the pathogenesis of T2DM are also varied, including the combination of risk factors such as age, obesity, sedentary lifestyle, environmental factors, or genetics (Prasad & Groop, 2015; Wu et al., 2014).

On the other hand, the complications of patients with T2DM are also quite varied, such as diabetic neuropathy, retinopathy, nephropathy, and cardiovascular disease. According to the data, about 40% of people with T2DM develop diabetic kidney disease, leading to chronic kidney disease (CKD), which contributes to half of new cases of end-stage renal disease (ESRD) each year (Gregg et al., 2014). In addition, people with T2DM have a 2-4 times higher risk of developing cardiovascular disease, which can lead to death (Jin & Ma, 2021). Several theories of pathogenesis complications in T2DM have been introduced, one of which is cell damage due to oxidative stress. This occurs when there is an imbalance between the production and elimination of reactive oxygen species (ROS) by the antioxidant system (Aranda-Rivera et al., 2022). When hyperglycemia occurs, ROS is overproduced through several mechanisms, such as mitochondrial dysfunction, labile glycation, glucose auto-oxidation, and intracellular polyol pathways (Bondeva & Wolf, 2014). Elevated glucose levels trigger the formation of advanced glycation end products (AGEs) that impact ROS production and activation of the inflammatory signal cascade. Ultimately, this chronic inflammatory process manifests as a diabetes complication (Mok et al., 2019). Chawla et al. stated in their study that the production of AGEs was observed to increase in individuals with hyperglycemia compared to healthy controls (Chawla & Kumar Tripathi, 2019).

Melatonin, also known as N-acetyl-5-methoxy-tryptamine, is a hormone produced by the pineal gland and is known for its antioxidant properties (Meng et al., 2017; Reiter et al., 2016). Melatonin has been widely researched and shown to have varying therapeutic effects and health benefits. Some of these are regulating human physiological rhythms, relieving sleep-related disorders, such as jet lag and insomnia, boosting the immune system, anti-aging and anti-inflammatory effects, as well as having anticancer activity (S. J. Chen et al., 2016);(F Li et al., 2013). Furthermore, melatonin also exhibits neuroprotective effects and facilitates the control of chronic diseases, such as cardiovascular disease, diabetes, and obesity (Agil, El-Hammadi, et al., 2015; Agil, Elmahallawy, et al., 2015);(Pandi Perumal et al., 2013). Several studies have shown that melatonin may play a role in various aspects related to T2DM. Some evidences suggest that melatonin may reduce diabetes complications by repairing oxidative damage. Pancreatic beta (β) cells are very susceptible to oxidative stress because they are known to produce endogenous ROS in high amounts and do not have much expression of antioxidant enzymes. Therefore, melatonin is believed to reduce diabetes complications, such as neuropathy, cardiovascular disease, and diabetic retinopathy (J. Wang & Wang, 2017). The high prevalence of T2DM and its complications, as well as the knowledge of the antioxidant effects of melatonin, prompted the authors to further review and provide updated references regarding the relationship of melatonin with T2DM. This review then discusses the bioactivity of melatonin, the dietary source of melatonin, and the role of melatonin in the pathophysiology of potentially therapeutic-related to the diseases in people with T2DM.

METHOD

This literature review sampled various relevant scientific studies published within the last 10 (ten) years. Literature searches were conducted through databases, such as *PubMed* and *Science Direct*, with the keywords "melatonin", "Type 2 Diabetes Mellitus", "pathophysiology", and "therapeutic potential". All studies discussing melatonin's bioactivity, melatonin food sources, melatonin's role in the pathophysiology of T2DM, and melatonin's potential as a therapy for T2DM were included in this study, while other studies that did not address the population and corresponding samples were excluded. The literature that met the inclusion criteria was analyzed systematically, and the results of the analysis were presented in the form of appropriate articles, tables, and diagrams to provide an understanding of the role of melatonin as a therapeutic potential for individuals with T2DM.

RESULTS

Researchers obtained 370 journal articles identified through five databases and screened through titles. Full-text articles that have been selected for eligibility are obtained totaling 31 journal articles. Furthermore, an assessment was carried out based on research articles that had met the inclusion and exclusion criteria, a total of 11 articles were obtained that could be used in the literature review contained in Figure 1. The results of the analysis and synthesis of 11 journal articles are in Table 1 as follows:

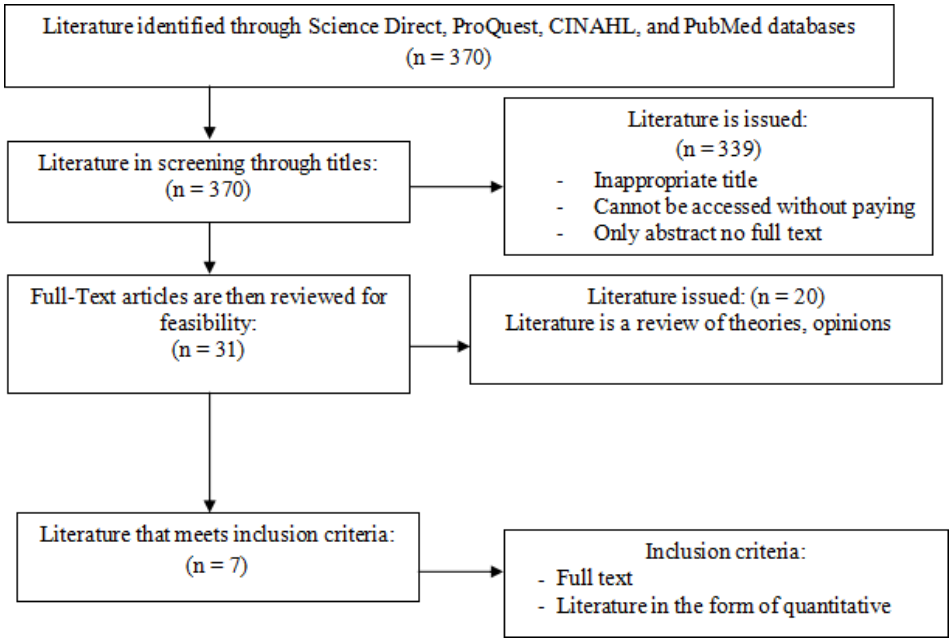

Figure 1. Diagram Literature

DISCUSSION

Bioactivity of Melatonin as an Antioxidant

Reaction Oxygen Species (ROS), or free radicals, play an important role in various physiological processes in the human body, such as regulating the circulation and respiratory system, erythropoietin production, and signal transduction. In addition, free radical compounds at certain levels can also increase cell survival by inducing cell proliferation and differentiation (Barton et al., 2016; Bielli et al., 2015). However, suppose the concentration of free radical compounds exceeds the required threshold to be beneficial. In that case, they can cause apoptosis and even cell necrosis through the mechanisms of DNA and RNA damage, protein denaturation, and lipid peroxidation, resulting in a range of health problems, including aging, inflammatory, carcinogenic, chronic metabolic diseases, neurodegenerative disorders, and sepsis (H. H. Chen et al., 2014; Paredes et al., 2014; A. K. Singh & Haldar, 2014; Zephy & Ahmad, 2015).

Therefore, in order to prevent and treat diseases caused by oxidative stress, many studies have discussed products that exhibit antioxidant activity and the ability to counteract free radicals, including melatonin (Deng et al., 2013); (A. N. Li et al., 2014; Y. J. Zhang et al., 2015). Melatonin is an indoleamine compound that is generally produced by the pineal gland in mammals during the nighttime, regulated by the suprachiasmatic nucleus of the hypothalamus and inhibited by light. However, several studies suggest that melatonin is also produced outside the pineal gland, unrelated to circadian rhythms, in organs such as in the digestive system, ovaries, lymphocytes, macrophages, retina, and skin (Tan, et al., 2015). The production of melatonin outside the pineal gland has a paracrine or autocrine effect, which affects the neuroendocrine hormone response, particularly in its capacity as a local antioxidant (Acuña-

Castroviejo et al., 2014; Tan et al., 2015). Melatonin is derived from tryptophan, which is converted into serotonin after hydroxylation and decarboxylation reactions. Serotonin is then converted to melatonin in two sequential reactions catalyzed by serotonin of *N-acetyl-transferase* (SNAT) and *N-acetylserotonin O-methyltransferase* (ASMT), with *N-acetyl serotonin* as an intermediate product. Several studies have proposed that mitochondria are the primary site of melatonin synthesis due to the presence of melatonin-forming enzymes, SNAT, and ASMT, as well as the 14-3-3 accessory protein, which prevents SNAT degradation and increases SNAT's affinity for serotonin (Reiter et al., 2018).

Figure 1 illustrates melatonin biosynthesis and the intracellular signal transduction pathway activated by stimulation of melatonin-specific receptors. The upper left shows the intracerebral site of melatonin biosynthesis, the pineal gland, while the lower left gives an idea of melatonin biosynthesis in mitochondria. As the illustration explains, melatonin is synthesized in the mitochondrial matrix but can also enter mitochondria via certain transporters. Then, melatonin activates specific MT1 and MT2 receptors on the outer membrane of mitochondria, inhibiting the production of MPTP and ROS and stimulating ETC and UCP by autocrine. The interaction of melatonin with specific MT1 and MT2 receptors and RZR/ROR receptors in the nucleus through the activation of different metabolic pathways is described on the right.

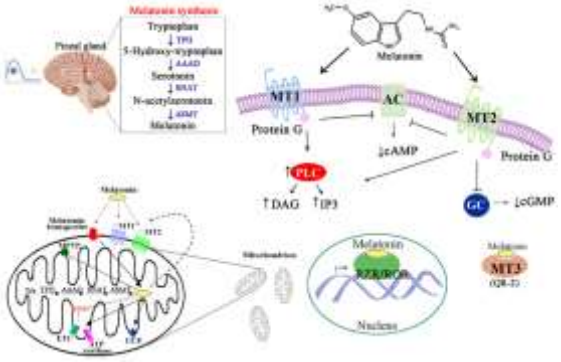

Figure 2. Biosynthesis and intracellular signal transduction pathway of melatonin

Description: AAAD, *aromatic L-amino acid decarboxylase*; AC, *adenylate cyclase*; AFMK, *N1-acetyl-N2-formyl-S-methoxykynuramine* (melatonin metabolite); ASMT, *N-acetylserotonin O-methyltransferase*; cAMP, cyclic adenosine monophosphate; cGMP, *cyclic guanosine monophosphate*; DAG, *diacylglycerol*; ETC, *electron transfer chain*; GC, *guanylate cyclase*; IP3, *inositol triphosphate*; MPTP, *mitochondrial permeability transition pore*; MT1-MT3, *melatonin specific receptor 1, 2, 3*; PLC, *phospholipase C*; QR-2, *quinone reductase 2*; ROS, *reactive oxygen species*; RZR/ROR, *retinoid Z receptor/retinoid acid receptor-related orphan receptor*; SNAT, *serotonin N-acetyltransferase*; TPH, *tryptophan hydroxylase*; UCP, *protein uncoupling.* Two factors limit the melatonin synthesis pathway: the lack of SNAT enzymes and the limited availability of tryptophan. Melatonin has a half-life of about 20 to 40 minutes and instantly diffuses into the blood and cerebrospinal fluid after being secreted. Due to its lipophilic and hydrophilic properties, melatonin diffuses easily through cell membranes. It can be detected in other body fluids, such as saliva, breast milk, sperm/semen, amniotic fluid, or in urine as *6-sulfatoxymelatonin* (aMT6), and the main metabolite of melatonin. The distribution of melatonin in the body is uneven, with its concentration higher in the cerebrospinal fluid than in the blood. Changes in blood melatonin levels, ranging from a few pg/mL during the day to 50-100 pg/mL at night, are considered to represent variations in levels throughout the body (Rzepka-Migut, 2020). An oral melatonin dose of 0.1-0.3 mg can reach a range of physiological concentrations, but higher doses (up to 10 mg) are also safe and have no adverse effects. The pharmacokinetic properties of melatonin preparations may vary and affect bioavailability: 1 to

10 mg can increase plasma melatonin levels from 3 to 60-fold from their normal peak (Costello et al., 2014).

The presence of melatonin has been shown to have a vital role in maintaining physiological balance in the human body. According to the results of the study, melatonin at 10 mg/kg was found to increase the efficiency of the electron transport chain in mitochondria in aged rates, reducing electron leakage and free radical formation (Meng et al., 2017). On the other hand, melatonin is also effective in interacting and collaborating with other reducing molecules, such as reductase and some non-enzyme-reducing agents, to maintain the body's normal balance. An in vitro study reported that melatonin's ability to scavenge hydroxyl radicals (·OH) is much higher than other reducing agents, such as vitamin E, glutathione, and mannitol. Melatonin also has a significant ability to inhibit vasoconstriction caused by hydrogen peroxide in the human umbilical artery. Besides quenching ROS/RNS, melatonin, and its metabolites can also modulate or capture other molecules, such as oxoferryl radicals derived from hemoglobin. Furthermore, in vitro and/or in vivo tests, melatonin has been shown to chelate toxic metals, such as cadmium, mercury, arsenic, lead, aluminum, and chromium, all of which are involved in the formation of free radicals (Hernández-Plata et al., 2015; Karabulut-Bulan et al., 2015; M. Li et al., 2016; Navarro-Alarcon et al., 2014; Y. Zhang et al., 2017). Melatonin may also stimulate the synthesis of other antioxidants, such as *gamma-glutamylcysteine synthetase* (γ-GCS), limiting the GSH synthesis enzyme rate in human vascular endothelial cells (ECV304). It also has been observed that under normal conditions, melatonin at a concentration of 1 nM can regulate the expression of antioxidant enzymes (AOE) in two types of nerve cells, thereby increasing the mRNA of *superoxide dismutase* (SOD) and *glutathione peroxidase* (GPx).

Several studies have reviewed various pathological conditions related to oxidative stress that can be addressed with the beneficial effects of melatonin. In vitro observations show that small doses (100 μM) of melatonin can reduce the oxidation of *low-density lipoprotein* (LDL), thereby inhibiting the course of atherosclerosis (Bonnefont-Rousselot, 2010). Melatonin therapy has also been proven to be effective in experimental models of hepato-pulmonary syndrome, where a study in Wistar rats demonstrated a decrease in vasodilation and pulmonary fibrosis, lipoperoxidation and oxidative stress, as well as an increase in the ratio of lung weight to body weight and changes in PCO2 and PO_2 after intraperitoneal administration of melatonin 20 mg/kg body weight for 14 days (Bosco et al., 2019). Melatonin supplementation may also aid in the treatment of thrombotic/hemolytic diseases associated with changes in the redox state. Experiments conducted on Swiss albino rats treated with 50 μM hemin (a hemoglobin degradation product) showed that administering 20 mg/kg body weight melatonin for 3 days helped reduce the amount of ROS and lipid peroxidation induced by hemin. Melatonin also increases GSH levels and increases the number of circulating platelets that will inhibit ferroptosis caused by ROS, a type of iron-mediated cell death, and platelet activation as well as reduce the amount of inflammatory cytokines IL-6, IL-23, TNF-α, and increasing the anti-inflammatory production of IL-10, thus reversing the effects of hemin (Naveen Kumar et al., 2019).

Melatonin Food Sources

Melatonin can be found in a wide variety of food ingredients, but there are significant differences in melatonin content between different types of food. For example, much higher level of melatonin was observed in legumes and medical plants than in other plant foodstuffs (Oladi et al., 2014). The uneven distribution of melatonin in animal and vegetable ingredients is due to different biophysical dynamic features in the individual constituent organs of animals or plants (Tan et al., 2014). In edible plants, fruits have the lowest melatonin content, while

seeds and leaves have the highest melatonin content. The concentration of melatonin in plant food products also depends on the environment in which plants are cultivated, such as temperature, duration of sunlight, ripening process, agrochemical treatment, and others (C. Wang et al., 2016). Therefore, it is important to clarify the factors affecting melatonin concentration in food to adopt an effective approach, such as seed germination, to increase melatonin content in the diet.

On the other hand, it is known that melatonin concentrations not only differ between species but also among different varieties of the same species. Therefore, variations in melatonin content may be caused by differences in extraction and detection techniques used and by modification of biosynthesis and metabolism of indoleamine compounds by different environmental conditions. Regarding the melatonin biosynthetic pathway, the process is similar between animals (humans) and plants, but there are several different factors that affect the melatonin content in these food sources (**Figure 2**) (Salehi et al., 2019).

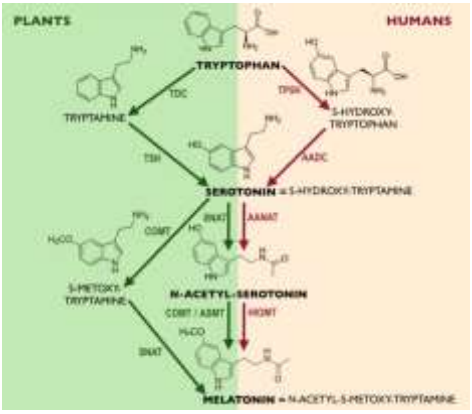

Figure 3. Comparison of melatonin biosynthesis processes in plants and humans/animals (Salehi et al., 2019)

Various plant-based food sources can be an alternative to melatonin sources, including cereals, fruits, vegetables, legumes and seeds, yeast, vegetable oils, etc. Cereals are one of the food ingredients that can be found widely worldwide. The data showed that an average of 96,5 ng/g and 16 ng/g melatonin content were obtained in corn and rice, respectively. Completing these findings, Setyaningsih et al. also reported that pigmented rice had a higher melatonin content, with non-gluten black rice having a melatonin content almost twice as high as glutinous rice and regular white rice. In addition, the same study also revealed that the melatonin content in rice that has been processed is only 1/3 of the melatonin content that can be found in whole rice (Setyaningsih et al., 2015). Melatonin is also found in commonly consumed fruits, such as grapes, cherries, and strawberries. The highest melatonin content in these three fruits ranged from 8,9 ng/g in grape skins, 13,46 ng/g in cherries, and 11,26 ng/g in strawberries. Other fruits are believed to contain melatonin at relatively low levels (Mercolini et al., 2012; Stürtz et al., 2011). The most studied vegetables for their melatonin content were peppers and tomatoes, with average concentrations of 11,9 ng/g and 14,77 ng/g.

Legumes and seeds, including white and black mustard seeds, have relatively high levels of melatonin, reaching 189 ng/g and 129 ng/g, respectively. Melatonin levels in legumes and seeds can increase significantly during germination, such as in germinated soybeans, which can increase melatonin levels by up to 400% compared to raw soybeans. The same thing occurs with germinated green bean seeds. On the other hand, coffee beans contain rich melatonin beverages because they contain very high levels, especially when roasted (Aguilera et al., 2015).

Melatonin is also found in juice, cocoa, balsamic vinegar but not in concentrates or teas, including green and black tea (Marcolini et al., 2012; Striith et al., 2011). Melatonin is also found in yeasts, especially *Saccharomyces cerevisiae*, which is widely used in bread making and the alcohol industry with a melatonin concentration of about 2,2 ng/g (Tan et al., 2015).

As for animal-based food sources, melatonin can be found in eggs, fish, and meat, with higher levels observed in eggs and fish compared to meat (Tan et al., 2015). In addition, humans can consume melatonin through the breast and other animal milks (Karunanithi et al., 2014; Tan et al., 2015). The melatonin content in breast milk is influenced by circadian rhythms similar to plasma fluctuations, with relatively low levels during the day and relatively high at night. Pumping breast milk at night can increase its benefits as a source of melatonin. During the nighttime, melatonin concentrations are estimated to be approximately ten times higher than during the daytime (Milagres et al., 2014). Melatonin is also detected in colostrum at concentrations comparable to plasma levels, which can be beneficial to newborns who experience melatonin deficiency in the first few weeks of life.

Role of Melatonin in the Pathophysiology of DMT2

Insulin is a hormone secreted by the human pancreas and is responsible for regulating blood glucose levels. The incidence of insulin depends on the activity of MT1 and MT2 receptors, where MT1 and MT2 acceptors are expressed in human pancreatic tissue so that melatonin can directly regulate the production of insulin or glucagon on the islets of Langerhans. When melatonin binds to its receptors and forms complexes with G(Gi) inhibitory proteins, an activated signaling cascade inhibits AC/cAMP and GC/cGMP pathways, decreasing cAMP levels (Mulder, 2017; Shah et al., 2021). The decrease in cAMP levels, which is a potentiator of insulin secretion, then results in a decrease in the secretion of the compound. However, melatonin may also increase secretion of inositol triphosphate (IP3) or glucagon via the Gq/11 signaling cascade that activates phospholipase C (Mulder, 2017);(Pesckhe et al., 2013 Melatonin levels tend to be low during the daytime when insulin secretion increases, and conversely, melatonin level increases at night, leading to decrease in insulin levels and an increase in glucose levels. Studies show that melatonin secretion decreases with age, and insulin resistance increases (M. Singh & Jadhav, 2014). Research indicates that melatonin also affects the growth and differentiation of pancreatic cells. Thus, it can be concluded that melatonin plays an important role in the insulin production in pancreatic β cells. The suppression of melatonin secretion due to night light exposure has been considered as a critical risk factor for DMT2 (Fonken & Nelson, 2014). An in-vivo study in mice demonstrated a functional link between melatonin and insulin, with the discovery that the lack of melatonin-infusing effect on insulin secretion could lead to elevated cAMP levels in mice with activated MT2 receptors, resulting in increased insulin secretion and greater pancreatic β cell mass. Therefore, MT2 receptors also contribute in the inhibition of melatonin on insulin secretion (Greenhill, 2016).

The pineal gland regulates the balance of blood glucose levels and insulin production by pancreatic β-cells, so patients with T2DM experience decreased melatonin levels in the body and increased melatonin membrane receptors (Tuomi et al., 2016). In this case, increased melatonin membrane receptor mRNA expression is thought to compensate for low melatonin levels in T2DM patients. Genetic factors, such as the G risk allele in the MTNR1B gene, also increase mRNA expression in β cells, reducing cAMP production, decreasing insulin secretion, increasing plasma glucose, and supporting the course of T2DM. Clinical studies show that melatonin may help control blood sugar by reducing fasting blood glucose levels but not increasing insulin secretion (Mok et al., 2019). In terms of the protective effect, melatonin plays

a role in preventing β-cells from functional damage in DTM2 (She et al., 2015). Recent studies have shown that removal of MT1 through pinealectomy can improve glucose intolerance and insulin resistance affecting the rhythm of daily blood glucose levels and increasing blood glucose concentrations at night. In the case of diabetes, hyperglycemia conditions increase the production of NADH and FADH2 and also inhibit the delivery of protons to complex III in the electron transport chain. Hyperglycemia means an increase in intracellular glucose concentration and then increased production of superoxide anion in non-insulin-dependent cells. As a result, the production of free radicals becomes uncontrolled and accumulates in the body. This oxidative stress can damage insulin signaling and disrupt insulin secretion, which can lead to insulin resistance and complications (Wan et al., 2013). According to some research studies, melatonin can help the treatment of diabetes and metabolic syndrome because it can provide anti-atherogenic effects (Lo, et al., 2017). Decreased melatonin levels can increase the risk of developing T2DM, particularly in women (Rybka et al., 2016). Melatonin deficiency can be one of the characteristics of DMT2 because melatonin production in diabetics that can be impaired due to hyperglycemia, as explained by Amaral et al. in their study (Amaral et al., 2014). Melatonin treatment can help lower fasting blood sugar levels, plasma leptin, and serum fatty acids and improve insulin resistance. However, melatonin treatment can also cause hypogonadism side effects in male due to changes in the hypothalamus circuit that controls reproduction (Oliveira et al., 2018).

Potential Therapeutics Melatonin as a Preventive Effort on DMT2 Complications

As is well known, DMT2 can cause some complications in patients, both microvascular and macrovascular. In this regard, melatonin is considered as a potential solution to prevent and therapeutic properties for various complications that may arise due to diabetes. Diabetic cardiomyopathy is one of the common complications of T2DM, defined as changes in the myocardium structure and function without other cardiac risk factors (Borghetti et al., 2018). Diabetic cardiomyopathy is characterized by increased myocardial fibrosis which can result in systolic dysfunction, then describes the inability of the heart to pump enough blood throughout the body, or commonly known as heart failure (Ahire et al., 2013); (Jia, et al., 2018). The main pathogenic factors in the development of diabetic cardiomyopathy are hyperglycemia, systemic insulin resistance, and impaired signaling of insulin metabolism in the heart. These factors trigger several pathways that lead to vascular endothelial dysfunction, adrenergic activity, impaired mitochondrial calcium handling, renin-angiotensin system activation, myocardial ischemia/functional hypoxia, oxidative stress, mitochondrial dysfunction, inflammation, endoplasmic reticulum stress, and cardiomyocyte death (Pourhanifeh, et al., 2020). The benefits of melatonin as an antioxidant have been proven effective in preventing heart damage due to T2DM, where melatonin can reduce oxidative damage to myocardial cells and inhibit extrinsic and intrinsic apoptosis pathways (Amin, et al., 2015). In an experimental study, melatonin can improve antioxidant status and reduce the level of lipid peroxidation as well as apoptosis markers in the heart tissue of diabetes-induced rats close to control values (Amin et al., 2015; Yu et al., 2017). Melatonin can also maintain mitochondrial function in the diabetic rat hearts by increasing mitochondrial biogenesis and deacetylation of mitochondrial antioxidant enzymes. This effect occurs through activation of the cGMP-PKGIα, SIRT1-PGC1α, and AMPK-PGC1α-SIRT3 signaling pathways (Amin et al., 2015). The activation of the PGC1α-SIRT3 signaling pathway is key in the cardioprotective action of melatonin, which can increase mitochondrial SOD activity, oxidative phosphorylation of complexes I, III, and IV, and reduce mitochondrial lipid peroxidation, ROS formation, and myocardial apoptosis (Amin et al., 2015).

Diabetic retinopathy is a diabetes-related microvascular complication that is a leading cause of vision loss in the working-age population (Das et al., 2012). In hyperglycemic conditions,

increased oxidative stress can cause thickening of the lower layer of the retina known as microangiopathy, that appears in diabetic retinopathy. In addition, because retinal tissue is rich in lipids, it is highly susceptible to oxidative stress. The condition of increased oxidative stress in diabetes also results in blood vessel leakage and increased permeability leading to the development of diabetic macular edema (Gundongan, et al, 1969;Mitshuhashi et l, 2013). The pathogenesis process of retinopathy in diabetes involves oxidative stress, inflammation and autophagy (Dehdashtian et al., 2018). Oxidative Stres can trigger inflammatory processes that result in retinal membrane structure and damage biomolecules that can trigger apoptosis and increase the expression of VEGF and matrix metallopeptidase 9 (MMP9). Inflammation can occur acutely or in the form of low-grade chronic inflammation that produces high amounts of leukocytes, causing capillary occlusion (Crooke, et al., 2017; Djordjevic et al., 2018). This condition can cause upregulation of VEGF in response to ischemic conditions and then trigger vascular dilatation, microaneurysms, neovascularization, blood-retinal barrier disorders, angiogenesis, and other vascular abnormalities. A study has detected markers, such as *thiobarbituric acid reactive substances* (TBARS) and advanced oxidation protein products (AOPP), which are the markers of lipid peroxidation and protein oxidation, respectively, in diabetic-induced mice and serum patients suffering from diabetic retinopathy. In addition, apoptosis of retinal neurons also occurs in pathogenesis because ganglion died cells that have a higher proportion of apoptosis cells (Djordjevic et al., 2018; Özdemir et al., 2014); (Yang et al, 2013). On the other hand, there is an increase in NO levels through upregulation of iNOS, which forms peroxynitrite, leading the production of malondialdehyde (MDA) through lipid peroxidation decomposition. High serum MDA levels support the hypothesis of increased toxic oxidative stress compounds (Kumar et al., 2014; Kumawat et al., 2014).

Diabetic neuropathy is defined as a set of common neurological complications of diabetic patients which include peripheral, autonomic, proximal and focal neuropathy. Peripheral neuropathy is the most common type and can progress to more serious conditions, such as foot ulcerations, gait disorders, amputations, and neuropathic pain (R. Singh, et al, 2014). There are several types of peripheral nervous system damage associated with diabetes, one of the most frequently occurring is *stocking-glove neuropathy* due to structural damage to axons and Schwann cells in the foot nerves. Several factors that induce diabetes include hyperglycemia, dyslipidemia, and insulin resistance that interact with each other. This event triggers activation of several pathological signaling pathways such as polyols, AGE production, protein kinase C (PKC), polymerase (PARP), poly (ADP-ribose), and hexosamine, leading to metabolic changes in the form of loss of insulin signaling, mitochondrial dysfunction, changes in gene expression and ion flow defects (increased Na^+ channel activity and decreased K^+ channel activity) along with oxidative stress and inflammatory processes leading to nerve damage and cell death (Feldman, et al., 2017); (Zenker et al., 2013). Some neuroactive substances are believed to play a role in the pathogenesis of diabetes-related neuropathy include changes in gamma-aminobutyric acid (GABA) and glutamate concentrations in the hippocampus (Jangra, et al., 2013)

An experimental study using a rat model demonstrated the effectiveness of melatonin in reducing dopaminergic fiber degeneration in the hippocampus. Another experimental study showed similar results that oxidative stress can damage a number of brain regions with a decrease in acetylcholinesterase activity and an increase in NAD and MDA. However, therapeutic intervention with melatonin supplementation has restored the recovery of NAD and MDA levels. On the other hand, melatonin has also been proven to reduce hyperglycemic conditions induced gliosis processes in some brain regions (Leeboonngam, et al., 2018; Metwally, et al., 2018). Moreover, melatonin significantly increases potent endogenous

antioxidants, Nrf2 and heme oxygenase-1, to reduce the ROS populations and suppress neuronal inflammation by reducing NF-κB activation (Ali, et al., 2018). Anti-apoptotic effects are also suggested through stimulation of PTEN-induced putative kinase 1 (PINK1) expression via MT2/Akt/NF-kB pathway (Onphachanh et al., 2017). Regarding metabolic changes, melatonin can prevent mitochondrial dysfunction and apoptosis in Schwann cells by upregulating Bcl2, NF-κB, mTOR, and Wnt signaling pathways (Tiong, et al., 2019). Increased insulin resistance, which is a pathological condition observed in T2DM patients, is thought to lead to worsening cognitive decline and neuropathy. Insulin resistance leads to endoplasmic reticulum stress, and melatonin administration has been shown to improve this condition by suppressing the ASK1 signaling pathway (Song & Kim, 2017). Research conducted by Seyit, et al. also proved that melatonin significantly increases the speed of nerve conduction and promotes Schwann cell proliferation in mice with diabetic neuropathy (Chang et al., 2014; Seyit, et al., 2016)

CONCLUSION

Hyperglycemia in T2DM leads to excessive ROS production, leading to an accumulation of oxidative stress and induction of insulin resistance. Oxidative stress is known to be associated with many other diabetes complications, such as cardiomyopathy, retinopathy, and diabetic neuropathy. Better treatment regimens are required to target pathogenic pathways associated with oxidative stress to improve this diabetic condition. Melatonin provides protection on diabetes through various mechanisms, such as enhancing antioxidant status, inhibiting apoptotic pathways, suppressing inflammation, and acting as a neuroprotective agent. Melatonin also plays an important role in glycemic control by reducing fasting blood glucose concentrations, improving insulin resistance, and increasing insulin sensitivity in cells. Therefore, melatonin supplementation can be used as a therapeutic measure to improve pathological conditions in patients and reduce the incidence of complications of T2DM.

REFERENCES

Acuña-Castroviejo, D., Escames, G., Venegas, C., Díaz-Casado, M. E., Lima-Cabello, E., López, L. C., Rosales-Corral, S., Tan, D. X., & Reiter, R. J. (2014). Extrapineal melatonin: Sources, regulation, and potential functions. *Cellular and Molecular Life Sciences*, *71*(16), 2997–3025. https://doi.org/10.1007/s00018-014-1579-2

Agil, A., El-Hammadi, M., Jiménez-Aranda, A., Tassi, M., Abdo, W., Fernández-Vázquez, G., & Reiter, R. J. (2015). Melatonin reduces hepatic mitochondrial dysfunction in diabetic obese rats. *Journal of Pineal Research*, *59*(1), 70–79. https://doi.org/10.1111/jpi.12241

Agil, A., Elmahallawy, E. K., Rodríguez-Ferrer, J. M., Adem, A., Bastaki, S. M., Al-Abbadi, I., Fino Solano, Y. A., & Navarro-Alarcón, M. (2015). Melatonin increases intracellular calcium in the liver, muscle, white adipose tissues and pancreas of diabetic obese rats. *Food and Function*, *6*(8), 2671–2678. https://doi.org/10.1039/c5fo00590f

Aguilera, Y., Herrera, T., Liébana, R., Rebollo-Hernanz, M., Sanchez-Puelles, C., & Martín-Cabrejas, M. A. (2015). Impact of Melatonin Enrichment during Germination of Legumes on Bioactive Compounds and Antioxidant Activity. *Journal of Agricultural and Food Chemistry*, *63*(36), 7967–7974. https://doi.org/10.1021/acs.jafc.5b03128

Ali, T., Rehman, S. U., Shah, F. A., & Kim, M. O. (2018). Acute dose of melatonin via Nrf2 dependently prevents acute ethanol-induced neurotoxicity in the developing rodent brain. *Journal of Neuroinflammation*, *15*(1). https://doi.org/10.1186/s12974-018-1157-x

Amaral, F. G., Turati, A. O., Barone, M., Scialfa, J. H., Do Carmo Buonfiglio, D., Peres, R.,

Peliciari-Garcia, R. A., Afeche, S. C., Lima, L., Scavone, C., Bordin, S., Reiter, R. J., Menna-Barreto, L., & Cipolla-Neto, J. (2014). Melatonin synthesis impairment as a new deleterious outcome of diabetes-derived hyperglycemia. *Journal of Pineal Research*, *57*(1), 67–79. https://doi.org/10.1111/jpi.12144

Amin, A. H., El-Missiry, M. A., & Othman, A. I. (2015). Melatonin ameliorates metabolic risk factors, modulates apoptotic proteins, and protects the rat heart against diabetes-induced apoptosis. *European Journal of Pharmacology*, *747*, 166–173. https://doi.org/10.1016/j.ejphar.2014.12.002

Aranda-Rivera, A. K., Cruz-Gregorio, A., Arancibia-Hernández, Y. L., Hernández-Cruz, E. Y., & Pedraza-Chaverri, J. (2022). RONS and Oxidative Stress: An Overview of Basic Concepts. *Oxygen*, *2*(4), 437–478. https://doi.org/10.3390/oxygen2040030

Barton, S. K., Tolcos, M., Miller, S. L., Roehr, C. C., Schmölzer, G. M., Moss, T. J. M., Hooper, S. B., Wallace, E. M., & Polglase, G. R. (2016). Ventilation-Induced Brain Injury in Preterm Neonates: A Review of Potential Therapies. *Neonatology*, *110*(2), 155–162. https://doi.org/10.1159/000444918

Bielli, A., Scioli, M. G., Mazzaglia, D., Doldo, E., & Orlandi, A. (2015). Antioxidants and vascular health. *Life Sciences*, *143*, 209–216. https://doi.org/10.1016/j.lfs.2015.11.012

Bondeva, T., & Wolf, G. (2014). Reactive oxygen species in diabetic nephropathy: Friend or foe? *Nephrology Dialysis Transplantation*, *29*(11), 1998–2003. https://doi.org/10.1093/ndt/gfu037

Borghetti, G., Von Lewinski, D., Eaton, D. M., Sourij, H., Houser, S. R., & Wallner, M. (2018). Diabetic cardiomyopathy: Current and future therapies. Beyond glycemic control. *Frontiers in Physiology*, *9*(OCT). https://doi.org/10.3389/fphys.2018.01514

Bosco, A. D., Schedler, F. B., Colares, J. R., Schemitt, E. G., Hartmann, R. M., Forgiarini Junior, L. A., Dias, A. S., & Marroni, N. P. (2019). Melatonin effects on pulmonary tissue in the experimental model of hepatopulmonary syndrome. *Jornal Brasileiro de Pneumologia*, *45*(3). https://doi.org/10.1590/1806-3713/e20170164

Chang, H. M., Liu, C. H., Hsu, W. M., Chen, L. Y., Wang, H. P., Wu, T. H., Chen, K. Y., Ho, W. H., & Liao, W. C. (2014). Proliferative effects of melatonin on Schwann cells: Implication for nerve regeneration following peripheral nerve injury. *Journal of Pineal Research*, *56*(3), 322–332. https://doi.org/10.1111/jpi.12125

Chawla, D., & Kumar Tripathi, A. (2019). Role of advanced glycation end products (AGEs) and its receptor (RAGE)-mediated diabetic vascular complications. *Integrative Food, Nutrition and Metabolism*, *6*(5). https://doi.org/10.15761/ifnm.1000267

Chen, H. H., Lin, K. C., Wallace, C. G., Chen, Y. T., Yang, C. C., Leu, S., Chen, Y. C., Sun, C. K., Tsai, T. H., Chen, Y. L., Chung, S. Y., Chang, C. Lo, & Yip, H. K. (2014). Additional benefit of combined therapy with melatonin and apoptotic adipose-derived mesenchymal stem cell against sepsis-induced kidney injury. *Journal of Pineal Research*, *57*(1), 16–32. https://doi.org/10.1111/jpi.12140

Chen, S. J., Huang, S. H., Chen, J. W., Wang, K. C., Yang, Y. R., Liu, P. F., Lin, G. J., & Sytwu, H. K. (2016). Melatonin enhances interleukin-10 expression and suppresses chemotaxis to inhibit inflammation in situ and reduce the severity of experimental

autoimmune encephalomyelitis. *International Immunopharmacology*, *31*, 169–177. https://doi.org/10.1016/j.intimp.2015.12.020

Costello, R. B., Lentino, C. V., Boyd, C. C., O'Connell, M. L., Crawford, C. C., Sprengel, M. L., & Deuster, P. A. (2014). The effectiveness of melatonin for promoting healthy sleep: A rapid evidence assessment of the literature. *Nutrition Journal*, *13*(1). https://doi.org/10.1186/1475-2891-13-106

Crooke, A., Huete-Toral, F., Colligris, B., & Pintor, J. (2017). The role and therapeutic potential of melatonin in age-related ocular diseases. *Journal of Pineal Research*, *63*(2). https://doi.org/10.1111/jpi.12430

Dehdashtian, E., Mehrzadi, S., Yousefi, B., Hosseinzadeh, A., Reiter, R. J., Safa, M., Ghaznavi, H., & Naseripour, M. (2018). Diabetic retinopathy pathogenesis and the ameliorating effects of melatonin; involvement of autophagy, inflammation and oxidative stress. *Life Sciences*, *193*, 20–33. https://doi.org/10.1016/j.lfs.2017.12.001

Djordjevic, B., Cvetkovic, T., Stoimenov, T. J., Despotovic, M., Zivanovic, S., Basic, J., Veljkovic, A., Velickov, A., Kocic, G., Pavlovic, D., & Sokolovic, D. (2018). Oral supplementation with melatonin reduces oxidative damage and concentrations of inducible nitric oxide synthase, VEGF and matrix metalloproteinase 9 in the retina of rats with streptozotocin/nicotinamide induced pre-diabetes. *European Journal of Pharmacology*, *833*, 290–297. https://doi.org/10.1016/j.ejphar.2018.06.011

Feldman, E. L., Nave, K. A., Jensen, T. S., & Bennett, D. L. H. (2017). New Horizons in Diabetic Neuropathy: Mechanisms, Bioenergetics, and Pain. *Neuron*, *93*(6), 1296–1313. https://doi.org/10.1016/j.neuron.2017.02.005

Fonken, L. K., & Nelson, R. J. (2014). The effects of light at night on circadian clocks and metabolism. *Endocrine Reviews*, *35*(4), 648–670. https://doi.org/10.1210/er.2013-1051

Greenhill, C. (2016). Risk Factors: Melatonin signalling implicated in the risk of T2DM. *Nature Reviews Endocrinology*, *12*(7), 374. https://doi.org/10.1038/nrendo.2016.85

Gregg, E. W., Li, Y., Wang, J., Rios Burrows, N., Ali, M. K., Rolka, D., Williams, D. E., & Geiss, L. (2014). Changes in Diabetes-Related Complications in the United States, 1990–2010. *New England Journal of Medicine*, *370*(16), 1514–1523. https://doi.org/10.1056/nejmoa1310799

Hernández-Plata, E., Quiroz-Compeán, F., Ramírez-Garcia, G., Barrientos, E. Y., Rodríguez-Morales, N. M., Flores, A., Wrobel, K., Wrobel, K., Méndez, I., Díaz-Muñoz, M., Robles, J., & Martínez-Alfaro, M. (2015). Melatonin reduces lead levels in blood, brain and bone and increases lead excretion in rats subjected to subacute lead treatment. *Toxicology Letters*, *233*(2), 78–83. https://doi.org/10.1016/j.toxlet.2015.01.009

Jameson, J. L., Kasper, D. L., Longo, D. L., Fauci, A. S., Hauser, S. L., & Loscalzo, J. (2020). *Harrison's Principles of Internal Medicine, Twentieth Edition*. McGraw-Hill Education.

Jia, G., Hill, M. A., & Sowers, J. R. (2018). Diabetic cardiomyopathy: An update of mechanisms contributing to this clinical entity. *Circulation Research*, *122*(4), 624–638. https://doi.org/10.1161/CIRCRESAHA.117.311586

Jin, Q., & Ma, R. C. W. (2021). Metabolomics in diabetes and diabetic complications: Insights from epidemiological studies. *Cells*, *10*(11). https://doi.org/10.3390/cells10112832

Karabulut-Bulan, O., Bayrak, B. B., Arda-Pirincci, P., Sarikaya-Unal, G., Us, H., & Yanardag, R. (2015). Role of Exogenous Melatonin on Cell Proliferation and Oxidant/Antioxidant System in Aluminum-Induced Renal Toxicity. *Biological Trace Element Research*, *168*(1), 141–149. https://doi.org/10.1007/s12011-015-0320-9

Karunanithi, D., Radhakrishna, A., Sivaraman, K. P., & Biju, V. M. N. (2014). Quantitative determination of melatonin in milk by LC-MS/MS. *Journal of Food Science and Technology*, *51*(4), 805–812. https://doi.org/10.1007/s13197-013-1221-6

Kumar, A., Chen, S. H., Kadiiska, M. B., Hong, J. S., Zielonka, J., Kalyanaraman, B., & Mason, R. P. (2014). Inducible nitric oxide synthase is key to peroxynitrite-mediated, LPS-induced protein radical formation in murine microglial BV2 cells. *Free Radical Biology and Medicine*, *73*, 51–59. https://doi.org/10.1016/j.freeradbiomed.2014.04.014

Kumawat, M., Kharb, S., Singh, V., Singh, N., Singh, S. K., & Nada, M. (2014). Plasma malondialdehyde (MDA) and anti-oxidant status in diabetic retinopathy. *Journal of the Indian Medical Association*, *112*(1), 29–32.

Leeboonngam, T., Pramong, R., Sae-ung, K., Govitrapong, P., & Phansuwan-Pujito, P. (2018). Neuroprotective effects of melatonin on amphetamine-induced dopaminergic fiber degeneration in the hippocampus of postnatal rats. *Journal of Pineal Research*, *64*(3). https://doi.org/10.1111/jpi.12456

Li, A. N., Li, S., Zhang, Y. J., Xu, X. R., Chen, Y. M., & Li, H. Bin. (2014). Resources and biological activities of natural polyphenols. *Nutrients*, *6*(12), 6020–6047. https://doi.org/10.3390/nu6126020

Li, M., Pi, H., Yang, Z., Reiter, R. J., Xu, S., Chen, X., Chen, C., Zhang, L., Yang, M., Li, Y., Guo, P., Li, G., Tu, M., Tian, L., Xie, J., He, M., Lu, Y., Zhong, M., Zhang, Y., … Zhou, Z. (2016). Melatonin antagonizes cadmium-induced neurotoxicity by activating the transcription factor EB-dependent autophagy–lysosome machinery in mouse neuroblastoma cells. *Journal of Pineal Research*, 353–369. https://doi.org/10.1111/jpi.12353

Lo, C. C., Lin, S. H., Chang, J. S., & Chien, Y. W. (2017). Effects of melatonin on glucose homeostasis, antioxidant ability, and adipokine secretion in ICR mice with NA/STZ-induced hyperglycemia. *Nutrients*, *9*(11). https://doi.org/10.3390/nu9111187

Meng, X., Li, Y., Li, S., Zhou, Y., Gan, R. Y., Xu, D. P., & Li, H. Bin. (2017). Dietary sources and bioactivities of melatonin. *Nutrients*, *9*(4). https://doi.org/10.3390/nu9040367

Metwally, M. M. M., Ebraheim, L. L. M., & Galal, A. A. A. (2018). Potential therapeutic role of melatonin on STZ-induced diabetic central neuropathy: A biochemical, histopathological, immunohistochemical and ultrastructural study. *Acta Histochemica*, *120*(8), 828–836. https://doi.org/10.1016/j.acthis.2018.09.008

Milagres, M. P., Minim, V. P. R., Minim, L. A., Simiqueli, A. A., Moraes, L. E. S., & Martino, H. S. D. (2014). Night milking adds value to cow's milk. *Journal of the Science of Food and Agriculture*, *94*(8), 1688–1692. https://doi.org/10.1002/jsfa.6480

Mok, J. X., Ooi, J. H., Ng, K. Y., Koh, R. Y., & Chye, S. M. (2019). A new prospective on the role of melatonin in diabetes and its complications. *Hormone Molecular Biology and Clinical Investigation*. https://doi.org/10.1515/hmbci-2019-0036

Mulder, H. (2017). Melatonin signalling and type 2 diabetes risk: too little, too much or just right? *Diabetologia*, *60*(5), 826–829. https://doi.org/10.1007/s00125-017-4249-8

Navarro-Alarcon, M., Ruiz-Ojeda, F. J., Blanca-Herrera, R. M., Kaki, A., Adem, A., & Agil, A. (2014). Melatonin administration in diabetes: Regulation of plasma Cr, V, and Mg in young male Zucker diabetic fatty rats. *Food and Function*, *5*(3), 512–516. https://doi.org/10.1039/c3fo60389j

NaveenKumar, S. K., Hemshekhar, M., Kemparaju, K., & Girish, K. S. (2019). Hemin-induced platelet activation and ferroptosis is mediated through ROS-driven proteasomal activity and inflammasome activation: Protection by Melatonin. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1865*(9), 2303–2316. https://doi.org/10.1016/j.bbadis.2019.05.009

Oladi, E., Mohamadi, M., Shamspur, T., & Mostafavi, A. (2014). Spectrofluorimetric determination of melatonin in kernels of four different Pistacia varieties after ultrasound-assisted solid-liquid extraction. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, *132*, 326–329. https://doi.org/10.1016/j.saa.2014.05.010

Oliveira, A. C. de, Andreotti, S., Sertie, R. A. L., Campana, A. B., de Proença, A. R. G., Vasconcelos, R. P., Oliveira, K. A. de, Coelho-de-Souza, A. N., Donato-Junior, J., & Lima, F. B. (2018). Combined treatment with melatonin and insulin improves glycemic control, white adipose tissue metabolism and reproductive axis of diabetic male rats. *Life Sciences*, *199*, 158–166. https://doi.org/10.1016/j.lfs.2018.02.040

Onphachanh, X., Lee, H. J., Lim, J. R., Jung, Y. H., Kim, J. S., Chae, C. W., Lee, S. J., Gabr, A. A., & Han, H. J. (2017). Enhancement of high glucose-induced PINK1 expression by melatonin stimulates neuronal cell survival: Involvement of MT2/Akt/NF-κB pathway. *Journal of Pineal Research*, *63*(2). https://doi.org/10.1111/jpi.12427

Özdemir, G., Ergün, Y., Bakariş, S., Kilinç, M., Durdu, H., & Ganiyusufoɬlu, E. (2014). Melatonin prevents retinal oxidative stress and vascular changes in diabetic rats. *Eye (Basingstoke)*, *28*(8), 1020–1027. https://doi.org/10.1038/eye.2014.127

Paredes, S. D., Forman, K. A., García, C., Vara, E., Escames, G., & Tresguerres, J. A. F. (2014). Protective actions of melatonin and growth hormone on the aged cardiovascular system. *Hormone Molecular Biology and Clinical Investigation*, *18*(2), 79–88. https://doi.org/10.1515/hmbci-2014-0016

Pourhanifeh, M. H., Hosseinzadeh, A., Dehdashtian, E., Hemati, K., & Mehrzadi, S. (2020). Melatonin: New insights on its therapeutic properties in diabetic complications. *Diabetology and Metabolic Syndrome*, *12*(1). https://doi.org/10.1186/s13098-020-00537-z

Prasad, R. B., & Groop, L. (2015). Genetics of type 2 diabetes—pitfalls and possibilities. *Genes*, *6*(1), 87–123. https://doi.org/10.3390/genes6010087

Reiter, R. J., Mayo, J. C., Tan, D. X., Sainz, R. M., Alatorre-Jimenez, M., & Qin, L. (2016). Melatonin as an antioxidant: under promises but over delivers. *Journal of Pineal Research*, 253–278. https://doi.org/10.1111/jpi.12360

Reiter, R. J., Tan, D. X., Rosales-Corral, S., Galano, A., Zhou, X. J., & Xu, B. (2018). Mitochondria: Central organelles for melatonins antioxidant and anti-Aging actions.

Molecules, *23*(2). https://doi.org/10.3390/molecules23020509

Rybka, J., Kędziora-Kornatowska, K., Kupczyk, D., Muszalik, M., Kornatowski, M., & Kędziora, J. (2016). Antioxidant effect of immediate-versus sustained-release melatonin in type 2 diabetes mellitus and healthy controls. *Drug Delivery*, *23*(3), 814–817. https://doi.org/10.3109/10717544.2014.917343

Rzepka-Migut, B., & Paprocka, J. (2020). Melatonin-Measurement Methods and the Factors Modifying the Results. A Systematic Review of the Literature. *International Journal of Environmental Research and Public Health*, *17*(6), 1916. https://doi.org/10.3390/ijerph17061916

Salehi, B., Sharopov, F., Fokou, P. V. T., Kobylinska, A., de Jonge, L., Tadio, K., Sharifi-Rad, J., Posmyk, M. M., Martorell, M., Martins, N., & Iriti, M. (2019). Melatonin in medicinal and food plants: Occurrence, bioavailability, and health potential for humans. *Cells*, *8*(7). https://doi.org/10.3390/cells8070681

Setyaningsih, W., Saputro, I. E., Barbero, G. F., Palma, M., & García Barroso, C. (2015). Determination of melatonin in rice (Oryza sativa) grains by pressurized liquid extraction. *Journal of Agricultural and Food Chemistry*, *63*(4), 1107–1115. https://doi.org/10.1021/jf505106m

Seyit, D. A., Degirmenci, E., & Oguzhanoglu, A. (2016). Evaluation of Electrophysiological Effects of Melatonin and Alpha Lipoic Acid in Rats with Streptozotocine Induced Diabetic Neuropathy. *Experimental and Clinical Endocrinology and Diabetes*, *124*(5), 300–306. https://doi.org/10.1055/s-0042-103750

Shah, N., Abdalla, M. A., Deshmukh, H., & Sathyapalan, T. (2021). Therapeutics for type-2 diabetes mellitus: a glance at the recent inclusions and novel agents under development for use in clinical practice. *Therapeutic Advances in Endocrinology and Metabolism*, *12*. https://doi.org/10.1177/20420188211042145

She, M., Laudon, M., & Yin, W. (2015). Melatonin receptors in diabetes: A potential new therapeutical target? *European Journal of Pharmacology*, *744*, 220–223. https://doi.org/10.1016/j.ejphar.2014.08.012

Singh, A. K., & Haldar, C. (2014). Age dependent nitro-oxidative load and melatonin receptor expression in the spleen and immunity of goat Capra hircus. *Experimental Gerontology*, *60*, 72–78. https://doi.org/10.1016/j.exger.2014.09.017

Singh, M., & Jadhav, H. R. (2014). Melatonin: Functions and ligands. *Drug Discovery Today*, *19*(9), 1410–1418. https://doi.org/10.1016/j.drudis.2014.04.014

Singh, R., Kishore, L., & Kaur, N. (2014). Diabetic peripheral neuropathy: Current perspective and future directions. *Pharmacological Research*, *80*, 21–35. https://doi.org/10.1016/j.phrs.2013.12.005

Song, J., & Kim, O. Y. (2017). Melatonin modulates neuronal cell death induced by endoplasmic reticulum stress under insulin resistance condition. *Nutrients*, *9*(6). https://doi.org/10.3390/nu9060593

Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B. B., Stein, C., Basit, A., Chan, J. C. N., Mbanya, J. C., Pavkov, M. E., Ramachandaran, A., Wild, S. H., James, S., Herman, W. H., Zhang, P., Bommer, C., Kuo, S., Boyko, E. J., & Magliano,

D. J. (2022). IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Research and Clinical Practice*, *183*. https://doi.org/10.1016/j.diabres.2021.109119

Tan, D. X., Manchester, L. C., Esteban-Zubero, E., Zhou, Z., & Reiter, R. J. (2015). Melatonin as a potent and inducible endogenous antioxidant: Synthesis and metabolism. *Molecules*, *20*(10), 18886–18906. https://doi.org/10.3390/molecules201018886

Tan, D. X., Zanghi, B. M., Manchester, L. C., & Reiter, R. J. (2014). Melatonin identified in meats and other food stuffs: Potentially nutritional impact. *Journal of Pineal Research*, *57*(2), 213–218. https://doi.org/10.1111/jpi.12152

Tiong, Y. L., Ng, K. Y., Koh, R. Y., Ponnudurai, G., & Chye, S. M. (2019). Melatonin prevents oxidative stress-induced mitochondrial dysfunction and apoptosis in high glucose-treated schwann cells via upregulation of Bcl2, NF-κb, mTOR, wnt signalling pathways. *Antioxidants*, *8*(7). https://doi.org/10.3390/antiox8070198

Tuomi, T., Nagorny, C. L. F., Singh, P., Bennet, H., Yu, Q., Alenkvist, I., Isomaa, B., Östman, B., Söderström, J., Pesonen, A. K., Martikainen, S., Räikkönen, K., Forsén, T., Hakaste, L., Almgren, P., Storm, P., Asplund, O., Shcherbina, L., Fex, M., … Mulder, H. (2016). Increased Melatonin Signaling Is a Risk Factor for Type 2 Diabetes. *Cell Metabolism*, *23*(6), 1067–1077. https://doi.org/10.1016/j.cmet.2016.04.009

Wang, C., Yin, L. Y., Shi, X. Y., Xiao, H., Kang, K., Liu, X. Y., Zhan, J. C., & Huang, W. D. (2016). Effect of Cultivar, Temperature, and Environmental Conditions on the Dynamic Change of Melatonin in Mulberry Fruit Development and Wine Fermentation. *Journal of Food Science*, *81*(4), M958–M967. https://doi.org/10.1111/1750-3841.13263

Wang, J., & Wang, H. (2017). Oxidative stress in pancreatic beta cell regeneration. *Oxidative Medicine and Cellular Longevity*, *2017*. https://doi.org/10.1155/2017/1930261

Wu, Y., Ding, Y., Tanaka, Y., & Zhang, W. (2014). Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *International Journal of Medical Sciences*, *11*(11), 1185–1200. https://doi.org/10.7150/ijms.10001

Yu, L., Gong, B., Duan, W., Fan, C., Zhang, J., Li, Z., Xue, X., Xu, Y., Meng, D., Li, B., Zhang, M., Zhang, B., Jin, Z., Yu, S., Yang, Y., & Wang, H. (2017). Melatonin ameliorates myocardial ischemia/reperfusion injury in type 1 diabetic rats by preserving mitochondrial function: Role of AMPK-PGC-1α-SIRT3 signaling. *Scientific Reports*, *7*. https://doi.org/10.1038/srep41337

Zephy, D., & Ahmad, J. (2015). Type 2 diabetes mellitus: Role of melatonin and oxidative stress. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, *9*(2), 127–131. https://doi.org/10.1016/j.dsx.2014.09.018

Zhang, Y. J., Gan, R. Y., Li, S., Zhou, Y., Li, A. N., Xu, D. P., Li, H. Bin, & Kitts, D. D. (2015). Antioxidant phytochemicals for the prevention and treatment of chronic diseases. *Molecules*, *20*(12), 21138–21156. https://doi.org/10.3390/molecules201219753

Zhang, Y., Wei, Z., Liu, W., Wang, J., He, X., Huang, H., Zhang, J., & Yang, Z. (2017). Melatonin protects against arsenic trioxide-induced liver injury by the upregulation of Nrf2 expression through the activation of PI3K/AKT pathway. *Oncotarget*, *8*(3), 3773–3780. https://doi.org/10.18632/oncotarget.13931.