The Role of Melatonin in Aging and Age-related Disorders

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Abstract

Aging as the main contributing factor of several chronic and degenerative diseases (DDs), is a consequence of genetic impairment through the lifespan, which disrupts the normal homeostasis of the human's body. The abnormalities of biological functions including protein homeostasis and transformed metabolites as well as cellular signaling cascades lead to health compromising disorders due to cellular senescence, apoptosis, transformation or uncontrolled proliferation. The human trials for the prevention of aging and age-related disorders (ARDs) relate to long time ago. The rising number of aged individuals in the population leads to target various molecules for both the prevention and treatment of aging and ARDs. Melatonin (Mel), secreted by pineal gland, is one of promising molecules, which attracts much attention for its anti-aging activities. This review focuses on the main endogenous contributing factors of aging and age- related disorders and the role of Mel on both the prevention and control of aging and ARDs in the individuals.

Keywords

Aging, ARDs, Melatonin, Degenerative diseases.

1. INTRODUCTION

Aging as the main contributing factor of several chronic and degenerative diseases (DDs), is the consequent result of many physiological as well as genetic impairments through the lifespan, which disrupts the normal homeostasis of the human's body and limits lifespan. The abnormal biological functioning which occurs throughout the aging process; including biological, biochemical and metabolic alterations, accelerates the development and quick progression of health compromising disorders due to cellular senescence, apoptosis, transformation or uncontrolled proliferation (Kowald, *et al*., 2016 ; Luu, *et al*., 2018 ; Tarocco, *et al*., 2019).

The human trials for the prevention of aging and age-related disorders (ARDs) relate to long time ago. The rising number of aged individuals in

Acute and chronic. Acute inflammation may be the system's initial reaction to hurtful stimuli. In chronic inflammation, the inflammatory reaction is out of proportion, causing harm to the tissues. Cyclooxygenase (COX) is a crucial enzyme in the synthesis of prostacyclins, prostaglandins, &thromboxane's, all of which are tangled in inflammation, platelet aggregation and pain (Pilotto *et al*., 2010). Vasoactive chemicals raise the permeability (pore size) of such arterioles, allowing blood cells, proteins, chemical substances and fluid to collect in that area. This fluid build-up causes swelling and can be painful because it compresses nerves in the site. Prostaglandins may also cause nerve irritation and contribute to pain(Grosser *et al*., 2011). Nonsteroidal antiinflammatory drugs (NSAIDs) are the most commonly prescribed medications worldwide (Virshette *et al*., 2019) and they are used to heal the acute & chronic pain caused by an inflammatory progression. NSAIDs are class of medications whose actions are all linked to COX inhibition in the release of prostaglandins and thromboxane (Pereira Leite *et al*., 2017) (Sostres & Lanas, 2016). The main pharmacology of NSAIDs is the central and peripheral inhibition of COX, affecting the translation of arachidonic acid into prostaglandins E2, thromboxane and prostacyclins. Both COX-1, COX-2, act in the body, are two enzymes involved in the action of NSAIDs. COX-1 is found in the majority of cells, including foetal /amniotic fluid and is involved in physiological functions as regulation and protection. COX-2 is triggered by inflammation and pro-inflammatory Cytokines (Patel *et al*., 2016). NSAIDs, or nonsteroidal anti-inflammatory drugs, have long been used in humans. As a consequence, long-term use of these drugs results in negative effects and harms human normal systems such as the hepatic and gastric system. As an outcome of adversative effects such as renal, cardiovascular, gastric lesions and gastrointestinal damage (Huerta *et al*., 2005) (Shih & Chang, 2007). Natural products (NPs) are biological compound/substance produced by analive entity (animals, microbes or plants) that possesses pharmacological activities and clinically beneficial in either raw or modified form (traditional remedies) (Goel *et al*., 2020). Traditional herbs and preparationsfor example, were regarded as drugs in the Ayurvedic medical system; the "Sushruta Samhita" (an Ayurvedic classic) contains approximately 700 plants for the treatment of 1100 ailments. A vast amount of information was provided by numerous traditional medical systems (Chinese materiamedica, Greek, Egyptian, Arab and Mesopotamian) as well as folk medicine (Ethnomedicine) and include Unani medicines as well. The separation of morphine from opium by Serturner (1804) marked the beginning of modern NP chemistry. Many of these discoveries resulted in the isolation of bioactive isolated chemicals as quinine (1820) derived from cinchona, cocaine (1859), strychnine (1818), penicillin, tubocurarine (1935) and other bioactive isolated compounds (Goel *et al*., 2020). Over 80% of approved therapeutic medicines were derivate of naturally occurring chemicals or were inspired by natural substance. The NPs have been extensively studied, and 33 percent of the 1394 small molecule approved drugs introduced between 1981 and 2019 were natural items or its derivates and 35 percent were built around pharmacophore from an NP (Newman & Cragg, 2020). Plants may synthesise a wide range of phytochemical constituents as secondary metabolites. Several phytochemicals have been used successfully in treatment of variety of human disorders. The World Health Organization (WHO) has attempted to identify medical plants used around the world,

the population leads to target the various molecules for both the prevention and treatment of aging and ARDs. Melatonin (Mel) secreted by pineal gland, is one of these promising molecules, which attracts much attention for its anti-aging activities. This review focuses on the main endogenous contributing factors of aging and age- related disorders and the role of Mel on both the prevention and control of aging and ARDs in tested individuals.

The main hallmarks of aging and ARDs:

There are variety of endogenous contributing factors, which ease the occurrence and progression of aging and ARDs and consequently gradual deterioration of normal physiological functions (Sveikata, et al., 2011). The major contributing factors are as follows:

1.1. Immune senescence:

Immune senescence, which is defined by decrease and deterioration in the competence of all the immune components, both the innate and acquired immunity, causes an increased incidence of cancer, infectious and DDs.

The weakened phagocytic activity and superoxide generation by phagocytic cells, decreased number of CD^{3+}/CD^{4+} cells, elevated number of CD^{8+} cells, and diminished humeral responsiveness are the well-known markers of aged individuals (Srinivasan, *et al*., 2005).

1.2. Oxidative stress:

Free radicals and oxidative stress is recognized as the key regulator of aging and ARDs (Garrido, *et al*., 2013). The findings of several experiments revealed that aging is correlated with deterioration of antioxidant system. The increased production of reactive oxygen species directs the cells toward death and consequently, augments the risk of tissue decline, aging and ARDs (Boga, *et al*., 2019).

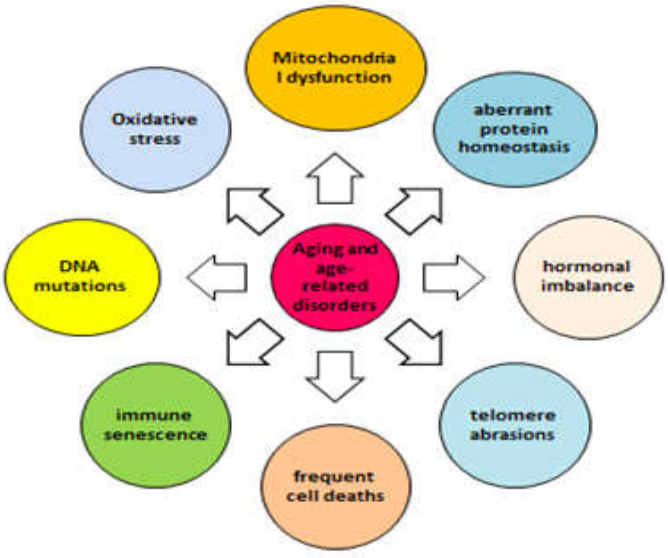

Fig-1. The main Hallmarks of aging and ARDS

1.3. Mitochondrial dysfunction:

There are a large number of studies, which have focused on the significance of mitochondrial dysfunction in occurrence and progression of aging and ARDs. As mitochondria plays critical role in several cellular regulatory processes including energy production, cell proliferation, cell cycle regulation, apoptosis, etc. therefore declined mitochondrial functioning cause oxidative stress, lower energy production, decreased mitochondrial membrane potential, and consequently aging and age-related physiological declines (Cadenas, *et al*., 2000 ; Arciuch, *et al*., 2012).

1.4. Abnormal hormonal secretion:

Accumulating number of data suggests the possible role of Pineal gland and *Mel*, a biogenic neuro- hormone releases at night and has long been associated with control of sleep, in the occurrence and progression of ageing (Reiter, *et al*., 1995; Josefson, *et al*., 2017). The identification of physiologic cross talk among this process, its regulators and associated mechanisms may help to either prevent or treat the accelerated aging and ARDs.

1.5. Aggregation of damaged proteins (ADPs):

ADPs is another contributing factor of aging and age-related neurodegenerative disorders. There is evidence suggesting the breakdown of protein quality control (PQC) systems contributes to aging. PQC is responsible for correct folding of protein which is essential for its function and prevention of incorrect interaction. Besides, PQC can sort aberrant proteins into distinct subcellular locations and it includes degradation system in order to clear the cell of damaged and aberrant proteins (Josefson, *et al*., 2017).

1.6. DNA damage:

It is assumed DNA damage has been the primary cause of aging. Evidence shows DNA damage is responsible for telomere dysfunction, genome instability, epigenetic alterations, mitochondrial dysfunction and proteostatic stress. Synthesis, folding, and degradation of protein are controlled by proteostatic pathways. DNA damage is one of the factors which induces proteostatic stress, resulting in protein misfolding and aggregation which in turn for many age related disorders such as Alzheimer's disease and Parkinson's disease (Schumacher. *et al*., 2021).

1.7. Telomeres abrasion:

Damaged cells that stop dividing and aggregate in the body as we age are known as senescent cells. They release SASP (Senescence Associated Secretion Profile), a group of factors which cause inflammation and reduce progenitor cell division (Childs. *et al*., 2015 ; Katzir, *et al*., 2021). The Telomeres may have a role in cellular senescence. Telomere shortening caused by lack of telomerase activity may have a role in determining several age-related organ features in human. Telomere loss has been linked to DNA damage. The link between cellular aging and telomeres shortening has long been known. Furthermore telomere attrition happens as people become older, and it's thought to be a key role in the aging process (Hornsby, *et al*., 2007; Xi, *et al*., 2013).

As mentioned previously, Mel as a biogenic neuro-hormone controls and modulates several physiological processes and since the present st-

udy may not describe all of them, so here we summarize the possible role of Mel in the management and prevention of aging and ARDs.

2. MATERIALS AND METHODS

2.1. Experimental

It is (C13H16N2O2); known as N-acetyl-5-methoxytryptamine, time keeping hormone, circadian, and sleep hormone, is a potent indolamine neuro-hormone which is mainly found in animals and released by the Pineal gland (Arnao, et al., 2018). This hormone, which was for the first time discovered on 1958 from the extract of bovine pineal gland, is produced by bacteria, fungi, protozoa, plants, invertebrates and various extra Pineal sites of vertebrates including retina, skin, gut, Harderian gland and leukocytes (Zhao, *et al*., 2019).

Mel is a derivative of tryptophan amino acid and its biosynthesized from serotonin which is catalyzed by two key enzymes, aryl-alkyl-amine N- acetyl transferase (serotonin N-acetyl transferase, AANAT) and hydroxy-indole-O-methyl transferase (HIOMT) in a sequential and species- dependent process (Peuhkuri, *et al*., 2012 ; Mannino, *et al*., 2021)

It acts via both receptor-mediated and receptor-independent mechanisms, which are interconnected with other pathways. There are different Mel receptor systems including MEL-1A-R, MEL-1B-R and MT3 subtypes; both membrane and nuclear receptors, present in animals, which demonstrate particular plasticity and modularity and are responsible for Mel biological activities (Tarocco, *et al*., 2019). Mel degrades via enzymatic, pseudo- enzymatic and free radical interactive processes. However, during oxidative stress the free radical pathway may dominates over the others (Emet, *et al*., 2018). Based on studies, the main function of it in early life forms (e. g, unicellular organisms) was free radical scavenging as an anti- oxidative agent (Sun, *et al*., 2016). As an antioxidant, Mel possess specific anti- oxidative properties, including its interaction with free radicals and to be produced under oxidative stress, which makes it a potent endogenous antioxidant that saves organisms from extreme oxidative stress (Tan, *et al*., 2015; Zhao, *et al*., 2015). During the process of evolution, Melatonin also functioned as signaling molecule to controlphotoperiodic information into hormonal output in multicellular organisms (Hardland, *et al*., 2010 ; Park, *et al*., 2011).

Moreover, this hormone controls the circadian multi-oscillator system activities including sleep/awake cycle, mood, environmental tolerance, blood pressure, immune functions, inflammatory responses, aging and ARDs, carcinogenesis and reproduction in a particular season through effects on central and peripheral clocks (Armstrong, *et al*., 1991 ; Shazia, *et al*., 2017 ; Rudiger. *et al*., 2018; Arnao, *et al*., 2018).

How Melatonin correlates with aging?

The key role of Mel in the management and prevention of aging and ARDs was stated (Poeggeler, *et al*., 2005) Based on recorded data, development and progression of aging and ARDs closely linked with dysfunction of inner molecular clocks, immune senescence and oxidative stress. Mel is the molecule, which regulates the circadian rhythm, remodels functions of immune system and acts as a potent free radical scavenger agent (Figure 2) (Zisapel, *et al*., 2018 ; Antonio, *et al*., 2013).

The findings of several studies revealed that the circulating levels of Mel is progressively declining over the life-span and various age-related degenerative and metabolic disorders such as de-

mentias, Alzheimer's disease (AD), Parkinson disease, ischemic and non- ischemic CVDs, diabetes, cancer etc. (Sandyk, *et al*., 2009 ; Cardinali, *et al*., 2019).

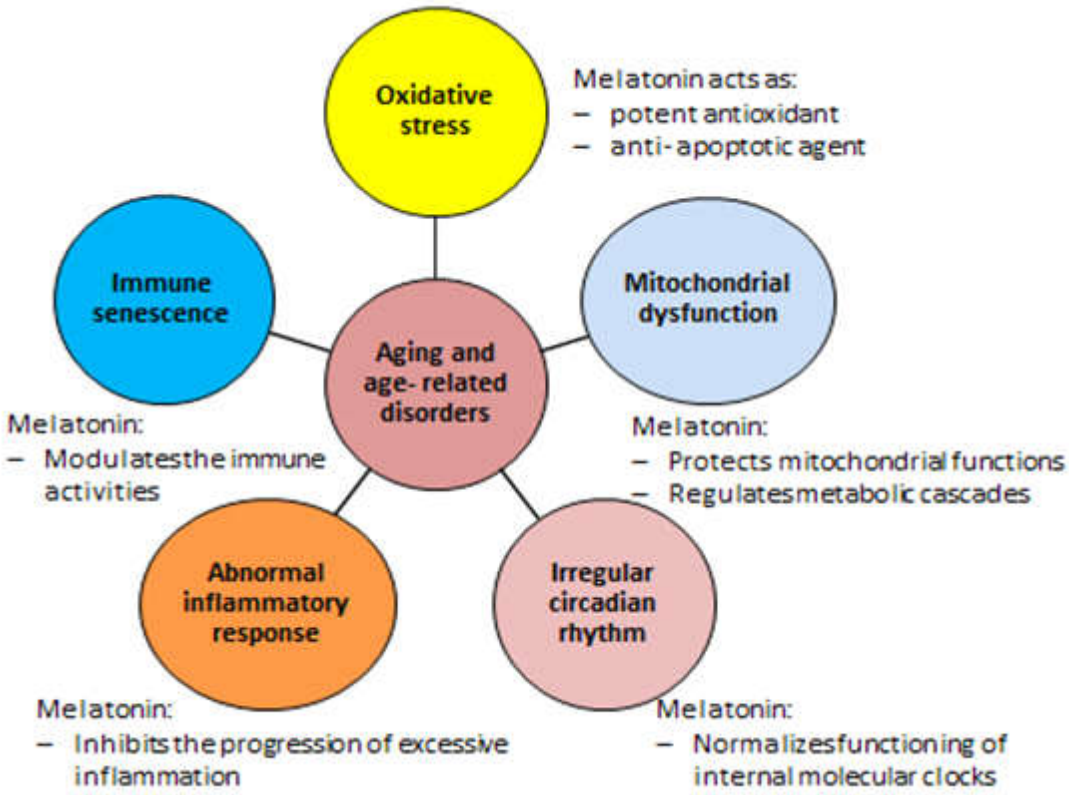

Fig. 2: The possible mechanisms of Mel anti- aging activities.

3. RESULTS AND DISCUSSION

In the light of literature reviving the declined level of circulating Mel negatively affects the physiologic functions controlled by inner molecular clocks 43. The importance of this precious harmon in regulation of circadian clock and its relation with aging was well cleared through the experiment, in which it had shown the association of gastrointestinal disorders (GIDs) and the aging process. The findings of this experiment was revealed that there is no relation between age and rhythmic expression of gut core clock genes whereas the transcriptome levels of immune components and biosynthesis of melatonin were less in colon of aged mice (Paulose, *et al*., 2018). In addition, the activity of sirtuin-1, which increases circadian amplitude, reduces during the aging and other ARDs and the inhibited activity of sirtuin-1 significantly reduces many effects of Mel (Hardeland, *et al*., 2019). Sirtuin-1 acts as an aging suppressor molecule, which helps in controlling the metabolism, proliferation of mitochondria, enhancement of circadian system functions etc.

It has been suggested that Mel is able to reduce the abnormal age-related symptoms and

extends the life span of animals with accelerated senescence whereas its efficiency for deceleration of normal aging process is poor (Hardeland, R., *et al*., 2017).

3.1. Literature Findings of Melaton

As per recorded data, the occurrence of insomnia and sleep disorders is common in aged individuals (Patel, *et al*., 2018). It is an important hormone to regulate the sleep-awake sequence (Jauhari et al., 2020). The excretion of Mel and its metabolite, 6-sulphatoxy Mel (6- SOM), is at their peak level during the night. However, the excretion of SOM is either lesser and/or delayed in elder insomniac people. Studies have shown that application of Mel improved the quality of sleep in affected individuals (Day, *et al*., 2018: Kleszczynski, *et al*., 2012). There is a non-benzodiazepine licensed pharmaceutical product called Prolonged-release (PR) Mel (Circadin®, Neurim Pharmaceuticals, Tel-Aviv, Israel) used for the treatment of primary insomnia in 55^{+} aged individuals. The effectiveness of this product is due to its mimicry effects of endogenous Melatonin, which improves the quality of sleep and morning alertness in insomniac patients. Moreover, the promising activity of exogenous harmone for improving the quality of sleep in peri- and post-menopausal women has been studied. Declined level of circulating Mel causes the sleep disorders including difficult initiation, maintenance, and repeated nocturnal and early morning awakening in these individuals. Application of Mel during this menopausal transition may improve the sleep disorder in women (Shazia, *et al*., 2017).

3.2. Neurodegeneration, Aging and Melaton

The association of oxidative stress, increased inflammatory responses and dysfunction of mitochondria with aging of brain and several neurodegenerative diseases is clear-ed (Jahari, *et al*., 2020; Hardeland, *et al*., 2016). Additionally, the negative effects of the declined level of endogenous Mel, which is synthesized in mitochondria of neurons and its relation with several neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), dementia etc. has been studied (Qi, Xueyan, *et al*., 2020 : Pozo, *et al*., 2010).It has been proposed that low level of Mel damages the homeostasis of mitochondria, which in turn results in release of mitochondrial DNA and activation of cytosolic DNA-mediated inflammatory response in nerve cells. It has been found that application of Mel reverses all the pathologic pathways that occur during the Huntington's disease (HD) in mice (Jauhari, *et al*., 2020).It was hypothesized that the AD patients have been experiencing many behavioral disturbances due to altered functioning of suprachiasmatic nucleus and Pineal gland, from where Mel is secreted. However, application of Melatonin has prevented the neurogeneration in AD and PD models (Cardinali, *et al*., 2019). The suggested hypothesis was approved by decreased concentration of it in CSF of AD patients (Meng, *et al*., 2017).

The antioxidant and cytoprotective properties of Mel mediates its anti- inflammatory activity, which may reverse cellular damages seen during aging and ARDs including neurodegenerative ones (Hardeland, *et al*., 2016). In addition, it is able to increase the removal of toxic proteins by the brain glymphatic system, hence reduces the progression of neurodegeneration (Cardinali, *et al*., 2019). Application of its exogenous activates the receptors, which in turn leads to modulation of cell transcriptome, enhanced expression of anti-

oxidant enzymes and down regulation of inflammation contributing enzymes including NO synthase, NADPH oxidase and pro-inflammatory cytokines (Haas, *et al*., 2019; Trifunovic, *et al*., 2008). Furthermore, the inhibitory effects of Mel on free RNS formation, mitophagy and activation of microglia, the central cell types that mediate the inflammation process in brain, may slow-down the physiologic aging of brain and cure the neurodegenerative diseases (Sandyk, et al ., 2009; Hardeland ; *et al*., 2016). While immune senescence, Inflammation, Aging and Melatonin are also the contributing factors of neuro degeneration.

Function remodeling of immune system is the central part of aging and ARDs. The immunomodulatory activity of Mel is proved since last time. Mel exerts its immune modulatory effects via both stimulation of release of pro-inflammatory mediators and suppression of inflammation-contributing processes including NO, COX-2, inflammasome NLRP3, gasdermin D, toll-like receptor-4, mTOR signaling, SASP, and amyloid-â. Additionally, Mel mediates the activation of sirtuin-1, increases the expression of NrF2, decreases the expression of NF-êB and IL—4/IL-10 release, which all are contributed to suppression of inflammation (Hardeland, *et al*., 2019)].

Melatonin modulates the immune activities by enhancing the generation of phagocytic as well as CD^{3+} cells whereas the hyperactivity of CD^{8+} cells are inhibited. Moreover, there is a positive change in the released cytokine profile of various immune cells. It has been stated that Mel most probably regulates the functionality of immune system through the immune-opioid network, touching G protein-cAMP signal pathway and intracellular glutathione (GSH) level (Srinvasan *et al*., 2005).

The Oxidative stress, Aging and Melatonin considering the importance of excessive ROS generation throughout the development and progression of aging and ARDs, it is suggested that strengthening of antioxidant defense, avoidance of ROS production and reduction of oxidative stress may be one way to decrease the rate of aging and ARDs (Garrido, *et al*., 2013).The significance of Mel as an anti- aging agent may well underline by the reduction of this natural antioxidant in the Pineal gland and down- regulation of its receptors, MT1 and MT2, in extraPineal tissues throughout the physiological aging. Administration of exogenous Mel may increase the longevity through protection of cells and cellular organelles against oxidative stress (Boga *et al*., 2019).

As an example, skin is one of the organs completely acts as an independent melatonergic system. Normally, Mel receptors are present in many dermatocytes and involved in hair cycling and fur pigmentation. The main extrinsic factor for the normal and accelerated aging process of skin is solar radiation (UV light), as in most cases it is associated with sunburns, immune suppression, aging of the skin and carcinogenesis (Day, *et al*., 2018).

The antioxidant and cytoprotective effects of Mel and its metabolites, which maintains the skin homeostasis and mitigate skin pathological processes including carcinogenesis, hyper proliferative and inflammatory states makes it an ideal molecule as a therapeutic choice (Kleszczynski, *et al*., 2012). As per reports, topical application of Mel - based creams in aged skins have improved the tonicity and hydration of the skin whereas the skin roughness was reduced significantly and reverse the signs of skin aging (Milani, M. and Sparavigna, *et al*., 2017).

One of the major cause of Mitochondrial dysfunction, Aging is due to the lacking of Melatonin

Mitochondrial dysfunction is considered as a major cause of aging and ARDs (Haas, Richard, *et al*., 2019). It has been shown that aging is correlated with accumulation of somatic mitochondrial DNA (mtDNA) and diminished function of respiratory chain (A and Larrson, *et al*., 2008).

The cardiovascular diseases (CVDs) including cardiac ischemic/reperfusion injury is one of the metabolic syndromes associated with decreased regeneration and turnover of mitochondria. During the progress of this pathologic scenario the affected cardiomyocytes are failed to maintain the biogenesis and homeostasis of mitochondria. The result of experiments done on the hypoxic/reoxygenated cardiomyocytes has shown that Mel treatment prolonged the survival of injured cardiac cells via recovery of mitochondrial biogenesis, through AMPK/PGC1á pathway, and inhibition of mitochondrial oxidative stress, which induces mitochondrial fusion and apoptosis (Qi, Xueyan, et al., 2020).

The anti-aging effects of Mel on the myocardial mitochondria of D-galactose- aged rats have investigated by Guo et al. The findings have revealed that Mel protects the mitochondrial functions in the tested animal model. The higher levels of phosphorylated compounds such as adenosine tri-, di-, and monophosphate (ATP, ADP, and AMP), and cytochrome C were the index of Mel effectiveness in the animal model of accelerated aging.

The reviewed literature also depicted that there are several pathological conditions such as high blood pressure, incontinence and changed gastrointestinal (GI) passage, altered contractile reaction of smooth muscles, etc. which are frequently happened in aged individuals.The findings of in-vitro experiments have shown the arterial tonicity in hypertensive and aged animal models decreases after application of Mel. It has been suggested that Mel reduces adrenergic release and increases cholinergic- induced relaxation (Pozo, *et al*., 2021). According to the in-vivo studies, Mel directly activates the Mel receptors and lessens the adrenergic tone. Additionally, the antioxidant activity of Mel and increased release of NO in Central Nervous System, also play important role in relaxation of arteries by Mel (Pozo, *et al*., 2021).

Impaired contractility of gallbladder smooth muscles is the consequent result of inflammatory process and oxidative stress (Portincasa, *et al*., 2004). The anti-inflammatory, antioxidant properties of Mel in addition to its effect on cholinergic release positively affect the smooth muscles contractibility, which in turn improves colonic passage time in patients with GI disorders including constipation predominant IBS (Siah, kewin Tien Ho, *et al*., 2014).

The regulatory effects of Mel for restoring the weakened contractility of detrusor muscles have studied in aged animals. It is thought that Mel normalizes the contractility of detrusor muscles through the regulation of calcium dependent and independent contraction, polarity of mitochondria, brain-related muscular functions and increased oxidative insult (Pozo, *et al*., 2021).

3.3.The role of Melatonin- rich diet in the prevention and management of aging and ARDs

The existence and production of Mel in variety of food stuffs have approved in Table 1.

(Mannino, Giuseppe, *et al*., 2021 ; Xiao, *et al*., 2017).). However, its content is greatly species-dependent. Studies have shown that nuts and medicinal plants have much higher content of Mel than other resources (Xiao, *et al*., 2017).The concentration of Mel in plant foods is influenced by the environmental conditions including the temperature, duration of sunlight exposure, ripening process, agrochemical treatment etc., under which the plants are cultured (Xiao, *et al*., 2017).

The importance of diet and nutritional supplements intake for improvement of health and promotion of healthy lifespan has been approved (Tresguerres, *et al*., 2014). The type of diet, which is consumed by individuals especially aged people, may influence the occurrence and progression of aging and ARDs in direct and indirect manner. The intake of Mel- rich diet could either normalize the concentration of endogenous Mel and thus, regulates the Mel-related functions or may influence the onset of aging and ARDs through modifying the production of Mel from its precursor, tryptophan (Peuhkuri, *et al*., 2012).

Table 1. Dietary sources of Mel

Food source	Examples	Reference
Animal sources	– Eggs	[59; 20]
	– Fish	
	– Meat	
	– Milk and dairy products	
	– Colostrum	
Plant foods	– Cereals (corn, rice, pigmented rice, wheat, barley and oats)	[59; 20]
	– Fruits (grapes, cherries, strawberries, pineapple, kiwi fruit, banana, apple, pomegranate,	
	– Vegetables (tomatoes, peppers, mushrooms)	
	– Legumes and seeds (white and black mustard seeds, soybean seeds, mung bean seeds)	
Nuts	– Pistachio	[59; 20]
	– Walnuts	
Juices and Beverages	– Beer	[59; 20]
	– Wine	
	– Coffee	
	– Cacao	
	– Balsamic vinegars	
Medical Plants	– Huang-qin (*Scutellaria biacalensis*)	[59]
	– St. John's Wort (*Hypericum perforatum*)	

Previously, it has been shown that this harmone positively regulates the bone mass. The result of studies on the effects of dietary supplementation on bone mass and its biochemical properties in aged- rats suggests that it improves the microstructure and biomechanical properties of bones in aged animal models (Tresguerres, *et al*., 2014).

The analysis of the result of consumption of Mel- rich diet, milk and sour cherries, on prevention and treatment of sleep disorders in children, adults, and elderly has indicated the potential of Mel- rich diet as adjuvants tor the prevention and management of sleep disorders (Magnanou, *et al*., 2009).

4. CONCLUSION

Nowadays, aging and ARDs including DDs which are the result of various physiological as well as genetic impairment through the lifespan, may lead to life threatening conditions such as cancer. Several promising candidate, including Melatonin, are being investigated for their anti-aging as well as aging preventive properties. It is well known endogenous indoleamine having many biological properties such as radical scavenging-, immune modulatory-, mitochondrial protective-, inner molecular clocks regulatory activities may serve as an ideal candidate for both the prevention and treatment of aging and several ARDs. Melatonin can be increased by extragenous administration of tryptophan containing foods and vegetables to regulate the sleeping process and facilitate the onset of age related disorders.

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