Nutraceutical Impact of Phytomelatonin on Health

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Abstract: Melatonin has been detected in a number of plant species evidenced that this classically-considered animal indole is actually both synthesized in and taken up by the plants. Phytomelatonin have been found in a variety of plant species and is known to act as antioxidant, growth promoter and to regulate photoperiodic responses and reproductive physiology in plants. Synthesis of melatonin in plants follows the pattern as in animals suggesting that the function of phytomelatonin might be analogous to animals as in plants. According to recent literatures, melatonin enhances the immunomodulatory function of different immune cells *via* secretion of activation signals i.e. cytokines, lymphokines, or more specifically interleukins. The purpose of this review is to encompass the interactions between cells of the immune system and understanding the root of immune deficiencies, and perceive potential avenues that the immune system can be modulated by melatonin/ phytomelatonin in the case of specific diseases for betterment of health.

Keywords: Phytomelatonin, Oxidative Stress, Immunity, Health

1. INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is a ubiquitous molecule in nature, having biological functions in unicellular organisms, fungi, plants and animals. The active research on melatonin was started after its discovery in the mammalian pineal gland in 1958 by Aaron Lerner et al. Melatonin has been detected in a number of edible plants proved that this classically-considered animal *indole* is actually both synthesized in and taken up by the plants. Synthesis of melatonin in plants (Phytomelatonin) follows the pattern as in animals' *i.e.* highest levels during the night of the light–dark cycle which suggesting the function of phytomelatonin might be analogous to animals as in plants. Phytomelatonin have been found in a variety of edible plants including medicinal species and is well known to act as antioxidant, growth promoter and to regulate photoperiodic responses and reproductive physiology in plants. It also involved in regulating numerous plant biological process including seed germination, vegetative growth, flowering, senescence, and response to stress (Paredes et al., 2009).

The similar structure of phytomelatonin (N-acetyl-5-methoxytryptamine) is an indole-amine derivative of the amino acid tryptophan. While melatonin is the term used for the compound of animal origin or obtained by chemical synthesis while the term phytomelatonin refers to the melatonin synthesis in plant. The term phytomelatonin was first proposed in 2004 in a research article treating the liver cancer in rat. The first information about endogenous phytomelatonin in higher plants was described in 1993 by *Van Tassel* and co-workers in a congress communication. The phytomelatonin might be identified by radioimmunoassay (RIA) and gas chromatography by mass spectrometry (GC-MS), HPLC-MS and liquid chromatography with mass identification (LC-MS/MS). Successive studies for quantification of phytomelatonin in many dietary plants are already well reported and now it has been widely accepted that phytomelatonin is present in all most all plants.

2. MELATONIN-IMMUNE SYSTEM INTERRELATIONSHIP

The immune system is a versatile defence system that has evolved to protect animals from invading pathogenic microorganisms and cancer. It is able to generate an enormous variety of cells and molecules capable of specifically recognizing and eliminating an apparently limitless variety of foreign invaders. These cells and molecules act together in a dynamic network whose complexity rivals that of the nervous system. This system is a truly amazing constellation of responses to attacks from outside the body. It has many facets, a number of which can change to optimize the response to these unwanted intrusions. The system is remarkably effective, most of the time. The immune system has a series of dual natures, the most important of which is self/non-self recognition. The others are general/specific, natural/adaptive=innate/acquired, cell-mediated/humoral, active/passive, primary/secondary. Parts of the immune system are antigen specific (they recognize and act against particular antigens), systemic (not confined to the initial infection site, but work throughout the body), and have memory (recognize and mount an even stronger attack to the same antigen the next time). Self/non-self recognition is achieved by having every cell display a marker based on the major histocompatibility complex (MHC). Any cell not displaying this marker is treated as non-self and attacked. The process is so effective that undigested proteins are treated as antigens.

The immune system is composed of many interdependent cell types that collectively protect the body from bacterial, parasitic, fungal, viral infections and from the growth of tumor cells. Many of these cell types have specialized functions. The cells of the immune system can engulf bacteria, kill parasites or tumor cells, or kill viral-infected cells. Often, these cells depend on the T helper subset for activation signals in the form of secretions formally known as cytokines, lymphokines, or more specifically interleukins. The purpose of this review is to encompass the cell types and interactions between cells of the immune system as a commentary on their importance and interdependence on the T helper subset. Such an understanding may help comprehend the root of immune deficiencies, and perceive potential avenues that the immune system can be modulated by melatonin/ phytomelatonin in the case of specific diseases.

The pineal gland is a well known regulator of seasonal changes in physiological functions of seasonal breeders (Pevet, 1985; Reiter, 1989). It is a neuroendocrine gland responsible for the transformation of external signals mainly photoperiodic information into a hormonal output, melatonin in a rhythmic fashion, characterized by a low level during the day and high during the night. This circadian rhythm of melatonin production is observed in all vertebrate species examined to date, regardless of their diurnal or nocturnal pattern of locomotor activity, indicating that melatonin's role in an organism is to provide information on darkness and not about nocturnal rest. Another essential feature of the diurnal rhythm of melatonin synthesis is its dependence on the length of the night period, thus the pineal gland may act as both "a clock of the day and a calendar of the Year" (Reiter 1993). Interpretation of the melatonin message within the body is essential to adapt the physiological functions of an animal to environmental conditions and needs, and this adaptation would increase the probability of its survival. Immune system activity is one of the physiological capabilities most responsible for the survival of an individual, whereas the survival of the species is guaranteed by reproductory system function.

3. BIOSYNTHESIS OF MELATONIN IN PLANTS

Tryptophan is a precursor for melatonin in St John's wort (*Hypericum perforatum* L. cv. Anthos) like in animals (Murch et al., 2000). Melatonin and phytomelatonin are synthesized from the precursor amino acid tryptophan, as the pathways that have been extensively studied in both animals and plants. However, the location of biosynthetic enzymes in plants is still undiscovered. In plants, tryptophan is converted into tryptamine by tryptophan decarboxylase (TDC). Tryptamine is then converted into 5-hydroxytryptamine (commonly known as serotonin) by tryptamine 5-hydroxylase (T5H). N-acetylation of serotonin is catalyzed by the enzyme serotonin N-acetyltransferase (SNAT). N-acetylserotonin is methylated by acetylserotonin methyl transferase (ASMT), a hydroxyindole-O-methyltransferase, which generates (phyto)melatonin.

4. MECHANISM OF ACTION OF MELATONIN ON IMMUNE CELLS

The molecular mechanisms responsible for the Pleiotropic effects of melatonin which involves mainly two actions: binding to high-affinity G-protein-coupled membrane receptors; and/or interaction with intracellular targets to modulate signal transduction pathways (Figure 1), redox-modulated processes, and the scavenging of free radicals (Hardeland et al., 2012). A large amount of evidence has been demonstrated the immunomodulatory capacity by exogenous melatonin administration in both *in vivo* and *in vitro* models (Carrillo-Vico et al., 2005). Few reports suggested that melatonin treatment promotes an increase in the weight of immune organs, both under basal and immunosuppressed conditions (Vishwas et al., 2013). Melatonin also modulates both the innate and specific immune responses through regulation of immunocompetent cell proliferation (Vishwas et al., 2012) and secretion of immune mediators, such as cytokines- IL-2, IFN-γ (Carrillo-Vico et al., 2006, Vishwas and Haldar, 2014). Thus, it can be speculate that phytomelatonin from dietary source, might be the have similar immunomodulatory function in *in vivo* models.

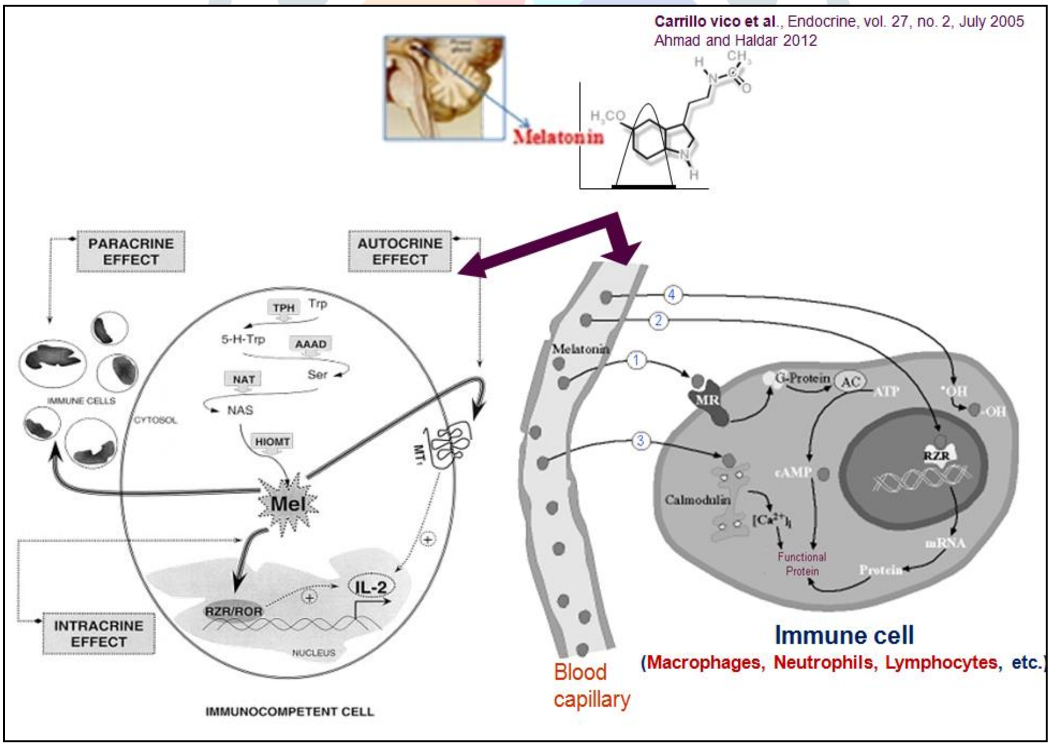

Figure **1.** Mechanism of action of melatonin in a immunocompetent cell

5. DIETARY SOURCES OF PHYTOMELATONIN

Phytomelatonin exists widely in many kinds of food stuffs. However, the content of phytomelatonin in foods exhibits huge differences from species to species. Much higher phytomelatonin was observed in nuts and medical herbs (Oladi et al., 2014). Additionally, in both animal foods and plant foods, melatonin could distribute unevenly in one individual animal or plant product because of the different biophysical dynamic features in organs (Tan et al., 2014). In many edible plants, fruits have the lowest melatonin content, while the seeds and leave have the highest melatonin content (Hardeland et al., 2006). Furthermore, the melatonin concentration in the plant food stuffs is also associated with the environment, cultivar of the species, including the temperature, sunlight exposing duration, ripening process, agrochemical treatment etc.(Wang et al., 2016).

Melatonin is present in a large number of edible plant species and values of phytomelatonin content are widely reported by Nawaz et al., 2016. The roots, seeds, leaves, bulbs, and flowers were found to be rich sources of melatonin in most of the plant species that already examined. Most of the plant species in which the presence of phytomelatonin has been reported belong to the families Rosaceae, Vitaceae, Poaceae, Apiaceae, and Brassicaceae. Further, the plants from few other families have also been reported earlier which possess melatonin in high amounts. The endogenous levels of melatonin also vary according to cultivars studied, and with the stage of fruit development (Feng et al., 2014). In a recent study it was reported that seed germination is associated with high concentration of melatonin suggested the authors that the germinated seeds of the edible food stuffs might be raise the melatonin levels in plasma (Aguilera et al., 2015). Moreover, the aromatic and medicinal plants have higher levels of phytomelatonin than seeds and fleshy fruits. However, leaves, stems, seedlings and roots presented higher phytomelatonin content than fruits.

6. ROLE OF PHYTOMELATONIN IN PLANTS

Phytomelatonin was proven to be ubiquitously synthesized in plant organs (Wang et al., 2014). Pleiotropic roles ranging from enhancing germination to delaying senescence of plants have already been reported (Wei et al., 2015). The role of phytomelatonin is enhancing growth and preserving the integrity of plants under stressful conditions. Roles of phytomelatonin have been reported as the regulator of circadian rhythm (Kolar et al., 1997), anti-oxidant as radical scavenger, auxin activity, and defense molecule against herbivores (Kim YJ et al., 2007). Further, melatonin binds with MT1 and MT2 receptors that are located on the plasma membrane in animals (Boutin et al., 2005) while, such receptors for phytomelatonin in plants are still a question. However, blast search with amino acid sequences of the melatonin receptors did not find any plant proteins, indicating that the plant melatonin receptor might be different with that of animals. Therefore, this suggested that anti-oxidation activity is the main function of melatonin seems to be purely chemical.

7. ROLE OF MELATONIN IN LIFE STYLE DISEASES

7.1. Diabetes And Phytomelatonin

Diabetes mellitus is a chronic disease characterized by elevated blood sugar levels. In diabetic patients, oxidative stress induced by the release of excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS) widely associated with chronic inflammation results potential tissue damage. Thus, complications due to Diabetes mellitus (such as retinopathy, nephropathy, neuropathy, ischemic heart disease, and peripheral vasculopathy) have most challenging health problems (Rochette et al., 2014; Prattichizzo et al., 2015). ROS and RNS are products of normal cell metabolism and have either beneficial or deleterious effects, depending on the concentration reached in the tissues (Dalle-Donne et al., 2006). Usually, the production and neutralization of ROS are balanced with antioxidants in a living system and do not cause any oxidative damage. The imbalance between these oxidants and antioxidants in the living organism, provoke an oxidative stress state, cause damage to cellular macromolecules, such as lipids, proteins, and nucleic acids (Jangra et al., 2013; Tangvarasittichai, 2015). The status of oxidant-antioxidant imbalance might be one of the mechanisms leading to the DNA damage detected in the lymphocytes of diabetic patients (Garcia- Ramirez et al., 2008; Woo et al., 2010; Kushwaha et al., 2011). Thus, phytomelatonin from the good source of dietary supplements might be play an important role in preventing oxidative DNA damage by increasing anti-oxidative property and scavenging excessive ROS and RNS that were generated in hyperglycemic conditions of Diabetes mellitus.

7.2. Sleep Disturbance and phytomelatonin

Sleep disturbance is common in children with atopic dermatitis, leading to impaired quality of life and have negative effects on neurocognitive function and behaviour. However, the pathophysiology of sleep disturbance in children with this disease is poorly understood, and there is no consensus on how to manage sleep problems. The pathophysiology of sleep disturbance is a very complex phenomenon which involves intertwined relationships between sleep, the circadian rhythm, the environmental stress, and the immunity. Phytomelatonin has a good safety measure having without adverse effects, making it a favourable choice for all age group and make possibility of best therapeutic approach.

7.3. Cancer and melatonin treatments

(Phyto)melatonin has a onco-static properties tested in different in vitro and in vivo experimental models of neoplasia. The effects of melatonin are mediated through both receptor-dependent and receptor-independent pathway. Melatonin receptors are present in plasma membrane and nuclear binding sites. Generally, melatonin is observed as anti-tumoral properties at pharmacological concentrations (between micro and millimolar). The effects of melatonin on tumors are mainly of two types, cytostatic and cytotoxic. Thus, cytotoxicity was examined exclusively at high melatonin concentrations. Therefore, the cancer cell type responses may differ at low or high levels melatonin content. For example, breast cancer cells are very effective at nanomolar melatonin concentrations and stopping their cell growth while others have no response. However, high melatonin concentration inhibits the proliferation colon cancer cells, and human prostate cancer cells. Further, no any cytotoxicity was observed in any non-tumoral cell, even at very high melatonin concentrations. This feature means that melatonin/phytomelatonin might be used against cancerous cells without causing any damage to healthy cells (Rodriguez et al., 2013).

7.4. Neurological disorders therapy and Phytomelatonin

Melatonin synchronizes the biological clock and maintains circadian rhythm of the body that we all have running 24 hours per day. Thereby it improves the normal physiology of the individuals by maintaining sleep-wake cycle, cognitive functions and immunity. If body's melatonin secretion drops off due to any reasons, the biological clock will also disturbed. Therefore, the impairment of the biological clock influences the neurodegeneration. The timed light-dark exposure therapy has very potential effect on restoration of biological clock in patients with neurodegenerative disorders. The oxidative stress and inflammation promotes clock disruption cause loss of synaptic homeostasis that provokes neurodegeneration. The timed light-dark exposure therapy might be a good option for the restoration of clock. The melatonin triggers the cycle of activation and repression of the master clock genes (Clock, Bmal1, and Rev-Erb, Per1, Per2, Cry1 and Cry2), thus instructing cellular functions and physiological outputs (Gaikwad, 2018). Further, phytomelatonin from the dietary stuffs might be a beneficial therapeutic approach to minimize such oxidative stresses and inflammations to overcome the situation from neurodegeneration due to clock impairement in an individual.

8. PHYTOMELATONIN AS A MASTER OF HEALTH: (A Therapeutic Approach)

Melatonin was initially thought to be exclusively produced in animals where melatonin was usually portrayed as a hormone. Recently, melatonin was well identified in plants and in the different parts of plants including roots, stems, leaves, flowers and seeds (Hattori et al., 1995). These findings have created a new area for melatonin research. The scientific reports of melatonin in plants have increased dramatically in the last few years (Hardeland, 2015; Fan et al, 2018). Further, one primary function of melatonin in plants are to protect plants from adverse environmental insults and reduce the effect of generated free radicals, since melatonin is a potent free radical scavenger (Tan et al., 2015). It is inevitable that phytomelatonin will enter the animals *via* the diet with melatonin-rich foodstuffs causes the increased serum melatonin level (Hattori et al., 1995; Meng et al., 2017). Also, it is known that physiological serum melatonin levels significantly enhanced the total antioxidant capacity in human (Benot et al., 1999), so it is likely that dietary melatonin from the medicinal plants or other melatonin-rich foodstuffs, protecting against oxidative damage in animals (Reiter and Tan, 2002). In addition, phytomelatonin have been found in a variety of plant species and is known to be as good promoter of antioxidant, growth, photoperiodic responses and reproductive physiology in plants (Paredes *et al;* 2009).

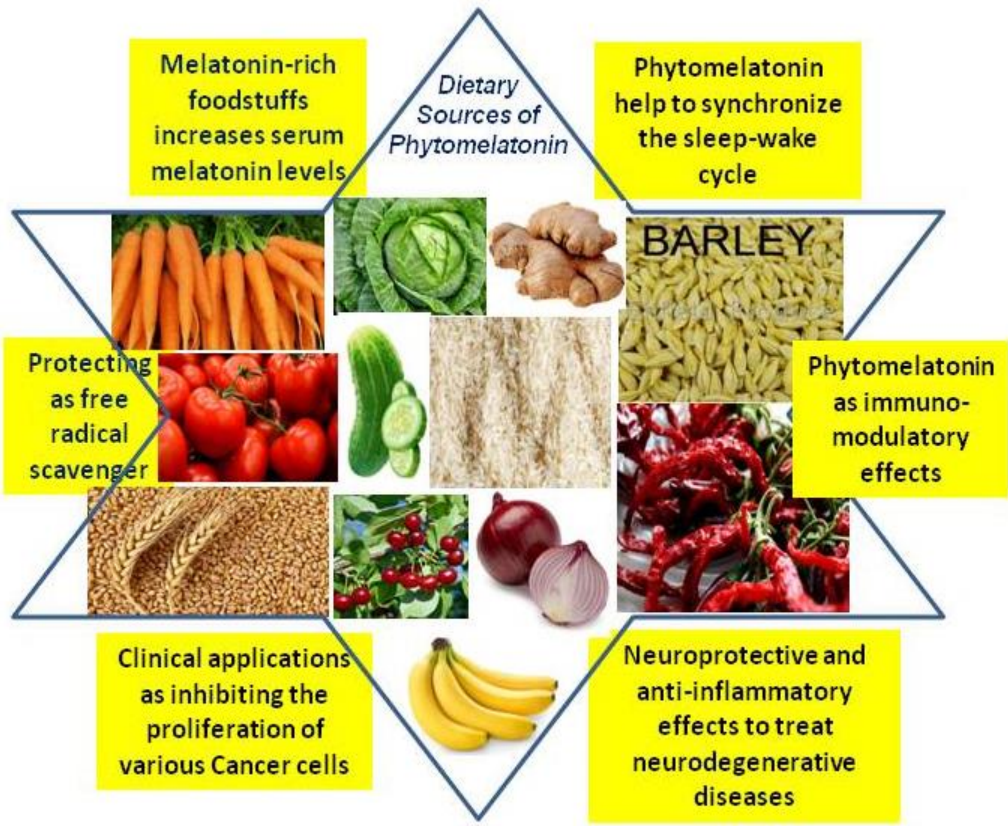

Figure **2.** A Therapeutic Approach of the Phytomelatonin

As a ubiquitous nature of melatonin has been reported in extremely high levels in most of the edible medical plants including many fruits and vegetables (Badria, 2002) such as banana, pineapple, strawberry, carrot, cabbage, corn, cucumber, ginger, onion, rice, tomato, etc. Epidemiological research indicate that consumption of fruit and vegetables can prevent against a variety of diseases (Doll, 1990) might be due to the preventative properties of vitamins C and E, β-carotene and flavonoids. However, plasma melatonin content might be increased in addition to endogenously produced melatonin after feeding phytomelatonin rich products and such phytomelatonin can bind to melatonin receptors in rabbit brain (Hattori *et al.*, 1995) which opens a new avenue of investigations with impact of phytomelatonin on health. Therefore, it has been clear that vertebrates can supplement their endogenous melatonin according to the plant material they consume. But still there has a question whether such phytomelatonin has any immunomodulatory function in humans. Thus, research needs for rich melatonin levels measured in different plants for medicinal purposes such immunomodulatory effect on animals which could help to explain their therapeutic action (Figure 2).

9. CONCLUSION

Hence, (phyto)melatonin was suggested to have a variety of clinical applications such as inhibiting the proliferation of various types of cancer cells (Ram et al., 2002) and exhibiting immunomodulatory properties (Vishwas et al., 2012). As a potent antioxidant and free radical scavenger, melatonin offers neuroprotective and anti-inflammatory effects to neuronal cells from free radical and neurotoxin-induced damage and displays potential therapeutic benefits in treating neurodegenerative diseases including Parkinson's disease, Alzheimer's disease, muscular sclerosis, stroke and neuroendocrine disorders (De Jonghe et al., 2010). Though, Melatonin is sold as a dietary supplement not as a drug at health food, other grocery stores and some drug stores.

The summary of literature made in the light of expression pattern of melatonin receptor in immune regulation. It became evident that this area of research received extremely less attention due to popularity of melatonin hormone in immune regulation of mammals including human being. In the present review work, I tried to draw the attention of the researcher towards the immune enhancement due to phytomelatonin as food stuff might be a drop in the ocean of knowledge about the immunity for better health.

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