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ARE THE MELATONIN SUPPLEMENTS POTENTIAL TREATMENT OPTIONS? A SYSTEMATIC REVIEW

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ABSTRACT:

Introduction: Melatonin is a neuro-hormone secreted from the pineal gland and involved in various regulatory activities in body. Ever-increasing use of melatonin supplements and enlarging research evidences make the authors undertook the review to arrive at a qualitative conclusion whether melatonin supplements can act as potential treatment options or not.
Methodology: A comprehensive search was undertaken in different electronic databases using various search terms. A total of 225 studies were identified including clinical research studies and basic experiments. Data were extracted individually from the studies and compiled in the end.
Results: Melatonin has been used successfully in chronic insomnia and as an anti-oxidant in cancer and other age-related neuro-degenerative disorders, especially Alzheimer's disease and Autistic disorders. Its evidences of use in other conditions remained insufficient and inconclusive.
Conclusion: Melatonin therapy may be considered as efficacious and safe in insomnia and as an anti-oxidant; however, other roles needs to be evaluated in further studies.

INTRODUCTION: Melatonin, also called *N*-acetyl-5-methoxytryptamine or N-[2-(5-methoxy-1H-indol-3-yl)ethyl] acetamide (systematic IUPAC name; **Figure 1**), is a naturally occurring neuro-hormone found in animals, plants, and microbes [1, 2]. In animals, circulating levels of melatonin vary in daily cycle, thereby allowing entertainment of circadian rhythms of several biological functions through activation of melatonin receptors [3] as well as due to its role as a pervasive and powerful antioxidant [4].

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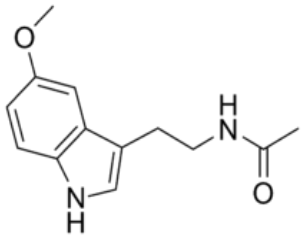

FIGURE 1: CHEMICAL STRUCTURE OF MELATONIN

Dietary supplements containing melatonin have been available over-the-counter (OTC) in the United States since mid-1990s as capsules, tablets or liquids, either sublingually or trans-dermal patches. In many other countries, sale of this neuro-hormone is not permitted without a prescription. It is illegal in some European member states but tolerated or authorised as a drug or dietary product elsewhere [5]. Bioavailability of melatonin is 30-50%.

Its metabolism is hepatic via CYP1A2 mediated 6-hydroxylation. Its half-life is 35-50 minutes and is excreted via urine [6]. Using significant dose-response models from literature clinical trial data or epidemiology, the BMD values were 0.4 mg/day for melatonin [7].

Melatonin has been on the front cover of magazines throughout the world for its claimed effects on ageing, cancer and many other health problems, opening up a vast potential market. Only its use in jet lag, sleep disorders and advanced cancer has been tested clinically (albeit scantily). Melatonin seems to alleviate jet lag symptoms, but that could be linked to its moderate hypnotic effect. The use of melatonin to treat major insomnia cannot be envisaged until its long-term safety has been proven. With this proviso, and if efficacy is confirmed in sufficiently large comparative trials, melatonin could prove useful for treating major sleep disorders in some patients, especially blind people and those with severe neurological disabilities.

According to open trials conducted by a single team, melatonin, alone or combined with interleukin-2, could slightly lengthen the survival of patients with some advanced cancers, but even partial tumour remissions are rare. All other "indications" are based on simplistic hypotheses or purely commercial considerations [5]. Melatonin supplements that are sometimes marketed for weight control or loss. Data suggest that long-term users of certain supplements experienced less weight gain than individuals who did not use the supplements.

Further study is necessary before recommendations regarding these supplements can be made [8]. Some products showed evidence of poor formulation and/or poor quality control as indicated by excessive friability, failure to disintegrate and dissolve, and excessive variation in hardness. In vitro release profiles of the two controlled-release products were substantially different. The poor quality of some supplements should be a concern to consumers and health care providers [9].

In addition to its' regulatory role, melatonin has antioxidative capacity, immunomodulatory potency, and also appears to be protective against a variety of cancers, especially breast cancer, although data is based mostly on observational studies and animal models [10-13]. Exogenous melatonin has been used for the treatment of sleep disorders of circadian origin such as jet lag and delayed sleep phase syndrome and as complement of other therapeutic drugs for the treatment of numerous diseases including glaucoma, irritable bowel disease, and certain types of cancers. Mainly to either enhance the therapeutic effect of conventional drug therapy or to reduce their toxicity thus ameliorating the side-effects [14-19].

Negative side-effects of exogenous melatonin in abovementioned clinical trials are rare. Melatonin has been detected in notable amounts for example in tomatoes, olives, cereals (barley, rice), walnuts, strawberry, olive oil, wine, beer, unprocessed cow milk, and night-time milk. Caffeine has both the stimulatory and inhibitory mechanisms affecting the levels of melatonin [20-31]. Tryptophan (Trp) supplementation promoted growth of cashmere goats by increasing daytime IGF-1 and night-time melatonin secretion [32]. S-adenosyl L-methionine (SAMe) is the natural, universal methyl group donor, participating in transmethylation reactions, known and commonly used as a dietary supplement and plays an important role in the synthesis of neuromediators and melatonin and mechanisms of epigenetic regulation [33].

Melatonin is a hormone secreted by the pineal gland, mostly in the dark period of the light/dark cycle, with corresponding fluctuations reflected in the plasma melatonin levels. This hormone plays a critical role in the regulation of various neural and endocrine processes that are synchronized with daily change in photoperiod. Abnormal melatonin levels are associated with metabolic disturbances and other disorders.

Melatonin potentially plays an important role in aging, prolongation of life span, and health in the aged individual. It may exert a beneficial action on neurodegenerative conditions in those with debilitating diseases. It interacts with metals and, in some cases, neutralizes their toxic effects.

Levels of melatonin decrease with aging in mice. Its dietary supplementation has recently been shown to result in a significant rise in levels of endogenous melatonin in serum as well as all other tissue samples tested.

This review was performed to evaluate whether melatonin therapy can be viewed as a dependable therapeutic measure in various clinical conditions in human beings on the basis of available research literature.

MATERIALS & METHODS:

1. **Eligibility:** Only peer-reviewed published papers on melatonin between 1975 to March, 2013 in English language on clinical studies (both observational and randomized trials) and experimental researches were taken into consideration. A total of 225 studies were identified including clinical trials and basic experiments.

2. **Information Sources:** Different electronic databases were searched for articles on melatonin including Cochrane, MEDLINE via PubMed, EMBASE, SIGLE, CAM, CAMPAIN, AMED, and CISCOM; however, no contacts were made with study authors to obtain information.

3. **Search strategy:** Electronic search was done in the databases using search terms like 'melatonin', 'melatonin therapy', 'melatonin supplements', 'melatonin clinical trials', 'experiments with melatonin', 'melatonin effects', 'melatonin use', 'melatonin in cancer', 'melatonin and ageing', 'melatonin and neurological diseases', 'melatonin anti-oxidant', 'melatonin and diabetes', 'melatonin and gut', 'melatonin and obesity', 'sleep and melatonin', 'circadian rhythm and melatonin', and 'melatonin and BP'.

4. **Data collection:** Data were extracted independently from each study papers or reports.

5. **Data items:** Data were sought with reference to number of participants involved, type of intervention (i.e. melatonin oral/injections), outcomes, and study design (observational, randomized, or basic experimental).

6. **Summary measures:** This study was aimed at only qualitative systematic review; no principal summary measure was used to combine or synthesize the results of studies.

7. **Risk of bias across studies and additional analyses:** Risk of bias (publication bias, selective reporting within studies) was not assessed in this study; only cumulative evidence is represented. No pre-specified additional analyses were performed.

8. **Reporting:** The PRISMA statement guidelines for reporting systematic reviews have been used in this study.

RESULTS:

Melatonin and circadian rhythm: High AST2 expression is induced by melatonin in the brain [34]. Findings further reveal an ancient evolutionary role for the prokineticin superfamily protein that links melatonin to direct regulation of the core clock gene feedback loops. The suprachiasmatic nucleus (SCN) serves as the ''master clock'' in the mammalian brain [35]. The SCN is reset on a circadian basis by light input from the retina during the day and by melatonin secretion from the pineal gland at night [36, 37].

Several animal studies have documented that melatonin is mainly synthesized and released during darkness, while the melatonin level is low in the presence of light [38]. This hormone is formed not only in the pineal gland but also in the photoreceptive structures of both vertebrates and invertebrates [39]. The melatonin synthesis pattern is known to reflect both daily rhythms and changes in photoperiod, demonstrating that melatonin has major roles in regulating both circadian and seasonal rhythms [40].

Several circadian rhythms, such as the rest/activity cycle, core body temperature, neuronal electrical activity and locomotor activity, are driven by melatonin [41-44]. However, melatonin does not directly induce immediate changes in clock gene mRNA expression in the rat SCN, suggesting that the phase-shifting effect of melatonin on the SCN molecular loop implicates a posttranslational rather than a transcriptional effect [40]. Little is known about the molecular mechanism by which melatonin drives the clock gene feedback loops in the SCN. In addition, the nocturnal increase in the circadian secretion of the cytokine IL-2 and its immunobiological activity are under melatonin control during the dark period [45].

There is a link between the rest/activity cycle and the immune system via melatonin-cytokine interactions [46]. Several studies imply a conserved role of melatonin as an important transducer of circadian information in invertebrates and vertebrates, and melatonin production has been demonstrated in the eyestalks of several crustacean species [47, 48].

The presence of MT2 melatonin receptors have not been conclusively shown in crayfish, but indirect evidences for such a receptor were presented by Mendoza-Vargas et al since the application of the MT2 receptor selective agonist 8-M-PDOT or antagonist DH97 had a significant effect on how melatonin affected the retinal photoreceptors [49]. Melatonin regulates the circadian rhythm and that this regulation is mediated by AST2 during the dark phase. AST2 acts as novel negative feedback regulator of CLK-BMAL1 activity [34].

Subnormal function of the biological clock with resultant reduced melatonin production has been linked to impaired maturation of the photendocrine system and of brown adipose tissue (BAT). The pineal gland of sudden infant death syndrome (SIDS) infants is smaller and less responsive to photoperiod stimulatory effects than the pineal gland of normal infants [50 - 52]. Thus plays an important role in regulating circadian rhythms [53, 54]. Another study provides strong evidence for a novel endocrine axis, involving the nutrient vitamin A regulated by photoperiod and melatonin and suggest a role for several new players in the photoperiodic neuroendocrine response. Melatonin is known to mediate the physiological effects of short-day photoperiod in mammals [55, 56].

Melatonin and sleep: Considerable number of evidences exists for the use of melatonin supplements for sleep problems in long-term care. While melatonin appears to have a modest positive effect on sleep quality among older adults [57-65], most studies were small in size, included only subjective assessments of sleep quality [66] except actigraphy or polysomnography, but caused statistically significant decrease in sleep onset latency, and increase in total sleep duration [67]. In addition, it is inconclusive whether melatonin poses risks to long-term care residents due to potential drug interactions [68, 69].

In hypertensive patients treated with beta-blockers, nightly melatonin supplementation significantly improved sleep quality, increased total sleep time, increased sleep efficiency, and decreased sleep onset latency as assessed by polysomnography, without apparent tolerance and without rebound sleep disturbance during withdrawal of melatonin supplementation. These findings may assist in developing countermeasures against sleep disturbances associated with beta-blocker therapy [70-76].

A recent clinical trial also concluded that exogenous melatonin was beneficial in improving sleep duration, quality and efficiency in healthy volunteers and might be of benefit in managing disturbed sleep [77]. Thus, there is considerable evidence to support the effectiveness of melatonin intervention for insomnia in adults, yet this intervention is underutilized.

Additional rigorous research is needed prior to making conclusive recommendations about the safety and risk-benefit of melatonin and appropriate management strategy for chronic insomnia [78, 79].

Melatonin as anti-oxidant: Melatonin was found to be a powerful free radical scavenger of radical oxygen and nitrogen species [80, 81] and wide spectrum anti-oxidant [82, 83] that can easily cross cell membranes [84] and blood brain barrier [81, 85, 86] and may attenuate or prevent oxidative stress [87] and lipid peroxidation [88, 89]. Melatonin administration has been shown to be of benefit in the prevention and attenuation of metal induced biochemical alterations [90, 91]. It does not undergo redox cycling, and once oxidized, cannot be reduced to its former state, hence called a terminal/suicidal anti-oxidant [92, 93].

A single molecule of N(1)-acetyl-N(2)-formyl-5-methoxykynuramine (AFMK), the first melatonin metabolite, can neutralize up to 10 ROS/NOS (reactive oxygen/nitrogen species) by the 'free radical scavenging cascade' [94]. Significant increase of total anti-oxidative status (TAS) level in plasma of multiple sclerosis (MS) patients has been observed with melatonin supplementation [95]. In animal models, melatonin has been demonstrated to prevent the damage to mitochondrial and nuclear DNA by carcinogens [97-101].

It has also been found to be effective in suppressing hepatocellular tumor-promoting activity of oxfendazole [102] and protecting against brain injury caused by ROS release in experimental hypoxic brain damage in newborn rats [103]. Few underpowered trials suggest that melatonin may enhance tumor response during treatment of breast cancer [104]. Melatonin supplementation during chemotherapy holds potential for reducing dose-limiting toxicities [105].

Melatonin's antioxidant activity may reduce damage caused by some types of Parkinson's disease, play a role in preventing cardiac arrhythmia and possibly increase longevity; it has been shown to increase the average life span of mice by 20% in some studies [106-108]. The administration of melatonin has also been shown to be of benefit in prevention and attenuation of renal scarring [109] and lowering of plasma lipids and homocysteine levels in animal models [109]. However, human studies are limited in this regard to date, and the evidence is insufficient to recommend melatonin supplements in subject with cancer or exposure to metals. Prospective, controlled clinical trials on safety and effectiveness of different therapeutic antioxidant strategies either individually or in combination are indispensable.

Melatonin and ageing: The impact of diet and specific food groups on aging and age-associated degenerative diseases has been widely recognized in recent years. The modern concept of the free radical theory of aging takes as its basis a shift in the antioxidant/prooxidant balance that leads to increased oxidative stress, dysregulation of cellular function, and aging. In the context of this theory, antioxidants can influence the primary "intrinsic" aging process as well as several secondary age-associated pathological processes. For the latter, several epidemiological and clinical studies have revealed potential roles for dietary antioxidants in the age-associated decline of immune function and the reduction of risk of morbidity and mortality from cancer and heart disease [110].

Enterochromaffin (EC) cells containing serotonin and melatonin may play a major role in maintaining gut function during ageing. The availability of gut serotonin and melatonin is increased in aged mice and melatonin treatment suppresses natural gastrointestinal production of 5-HT and melatonin in the aged mouse intestine [111]. Thymic re-growth and reactivation of thymic functions may be achieved in old animals by different endocrinological or nutritional manipulations such as treatment with melatonin. Melatonin may also act through specific receptors on T-cells [112].

Melatonin potentially may play an important role in aging, prolongation of life span, and health in the aged individual [113, 114]. Levels of melatonin decrease with aging in mice. Melatonin supplementation has no significant effect on cerebral cortical levels of nitric oxide synthase or synaptic proteins, such as synaptophysin and SNAP-25. Notably, however, elevated brain melatonin levels resulted in a significant reduction in levels of toxic cortical Aβ of both 40 and 42 amino acid forms. Taken together, these results suggest that dietary melatonin supplementation may slow the neurodegenerative changes associated with brain aging and that the depletion of melatonin in the brain of aging mice may, in part, account for this adverse change [115].

Evidence has indicated that increasing the endogenous antioxidants defence system and modulation of free radical production by dietary restrictions contribute to increased longevity in animal models. Thus, increasing dietary intake of antioxidants is believed to increase longevity. Earlier studies have shown some increase in median life span in animal models. It was found that supplementing middle-aged (18 months) C57/BL mice with various antioxidants had no effect on longevity as measured by the average age of death. Therefore, dietary antioxidant supplementation seems unlikely to increase longevity when begun in middle age; supplementation started in early life might be more effective [116].

Supplements with unproven mixtures of antioxidants or hormones, such as melatonin with antioxidant properties, are widely recommended and cover a big market. However, we are far away from understanding their specific role and we have to consider that, based on the free radical theory of aging, the balance of antioxidants and pro-oxidants in both directions is of importance in maintaining the physiological function of both reactive oxygen species and antioxidants [117].

Melatonin and neurological conditions: Clinical studies have demonstrated abnormalities in melatonin production or release in individuals with Autism Spectrum Disorder (ASD) [118, 119]. One study concluded that unaffected parents of individuals with ASD have lower melatonin levels, and that the deficits were associated with low activity of ASMT gene, that encodes enzymes of melatonin synthesis [118]. Large effect sizes were obtained from randomized trials [120, 121]. Melatonin was found to decrease sleep latency and increase total sleep time, without any significant effect on the number of night-time awakenings [122].

Till date, no official guidelines exist for the use of melatonin in children with ASD. It has been suggested as promising Grade A treatment, but off-label (i.e. not FDA approved) for autism spectrum disorder [123]. Further studies exploring these treatments are needed. A total of 45.6% in individuals with ASD were found taking some form of psychotropic agents, including St. John's wort and melatonin [124]. Physicians treating children with an ASD should make it standard practice to inquire about each child's possible use of these types of treatments.

Melatonin may influence the symptoms of Parkinson's disease and/or the effectiveness of dopaminergic therapy. Preliminary evidence suggests that it may also influence non-motor symptoms of PD, such as respiratory disorders, gastrointestinal disorders, mood disorders, sleep and orthostatic hypotension. Whenever possible, clinicians should ensure that complementary therapy is used appropriately in PD patients without reducing the benefits of dopaminergic therapy [125]. Strategy based on melatonin supplements has been proposed to at risk parents of schizophrenia to eliminate the disorder [126].

Decreased serum level of melatonin has been suspected to be involved in Alzheimer-like tau hyperphosphorylation [127-129].

Melatonin supplements are able to reverse AD pathology and memory deficits in many animal experiments and clinical trials. However, the underlying mechanism regarding how melatonin rescues the AD-like memory/synaptic disorder remains unknown. Melatonin was found to rescue the EPACs/miR-124/Egr1 signal pathway, important in learning and memory [130], and is proposed to attenuate the synaptic disorder and could benefit drug discovery in neurodegenerative diseases [130].

Melatonin supplementation did not significantly change cerebral cortical levels of nitric oxide synthase or synaptic proteins such as synaptophysin and SNAP-25. Increased brain melatonin concentrations however, led to a significant reduction in levels of toxic cortical Aβ of both short and long forms which are involved in amyloid depositions and plaque formation in Alzheimer's diseases. Thus, melatonin supplementation may retard neurodegenerative changes associated with brain aging [131]. A case study revealed that melatonin-treated (6 mg/day) identical twins had less memory loss over 36 months [132].

Another small study showed improvement in mood and memory over 6 days in 10 patients with mild cognitive impairment receiving 6 mg melatonin daily [133]. In other studies, melatonin doses (6-9 mg/day) to sleep-disordered AD patients over 22-35 months prevented typical cognitive decline [134, 135], but lower doses (3 mg/day) failed to resist such decline [136]. Nevertheless, the studies evaluating role of melatonin in AD were small and of poor quality [137]; thus clinical value of melatonin for prevention and treatment of Alzheimer's disease remains ambiguous, and will remain so until properly designed human trials have been performed [137].

Melatonin supplementation effects were tested on dietary intake, growth and development of children with ADHD treated with Ritalin that improved height and weight growth of children. These effects were attributed to circadian cycle modification, increasing sleep duration and the consequent more growth hormone release during sleep [138].

Melatonin has either multiple-cited recommendation for use in epilepsy, but paradoxically often has a proconvulsant effect in addition to potentially serious adverse effects [139]. While a study reported reduction in mean seizure frequency [140], few reported increase in seizure [141-143]. Thus melatonin appears to have unpredictable effects on seizure frequency, and should be used with caution in patients with epilepsy [144]. Patients should be inquired as to the nature of any alternative medicine products they are using, with the view

that these products may be reasonable if traditional antiepileptic drug therapy is continued, potential adverse effects of the alternative agents are monitored, and the alternative and traditional agents do not conflict [139].

Melatonin supplementation has been shown to lessen spinal cord injury (SCI), but its use has been limited by its side effect profile [145]. In an experimental work, rats underwent a moderate-to-severe contussional SCI with placebo or beta-methyl-6-chloromelatonin, 10mg/kg or 100mg/kg supplementation. The 10mg/kg supplementation demonstrated benefit, while the latter was limited by toxicity. In another experimental work, the protective effect of exogenous melatonin or 6-hydroxylmelatonin on neurons was examined in N2a cells following exposure to oxygen-glucose-serum deprivation insults. The results showed that both reduced apoptosis, but they could not completely inhibit the apoptosis of the cells and the inhibitory effect of melatonin was stronger than that of 6-hydroxylmelatonin.

Both of them could inhibit LDH and cytochrome C release and caspase 3 activities. So, both were proposed to be used as supplements in the treatment of neurological disorders involving oxidative stress. Melatonin serves as more than a ROS scavenger and its other roles await further study [146]. Another experiment determined if the loss of endogenous melatonin via pinealectomy affected rat CA1 and CA3 pyramidal neuron numbers over a 20-month span. Since pinealectomy eliminates many neurohormones, some rats received daily melatonin supplementation to determine if this would reverse its effects. Pinealectomy caused oxidative stress and a subsequent compensatory change in the glutathione system. These results indicate that endogenous melatonin is neuroprotective [147].

A randomized, double-blind, placebo-controlled trial has been performed in 25 elderly subjects with mild cognitive impairment (MCI). These subjects were randomly assigned to supplement their diet with either an oily emulsion of docosahexaenoic acid (DHA)-phospholipids containing melatonin and tryptophan (11 subjects) or a placebo (14-matched subjects) for 12 weeks. Older adults with MCI had significant improvements in several measures of cognitive function when supplemented with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan for 12 weeks, compared with the placebo [148].

The correlation of serum melatonin levels and curve progression in adolescent idiopathic scoliosis, and the effects of melatonin therapy in scoliotic patients with reduced levels of endogenous melatonin were studied in 40 adolescent patients with moderate to severe idiopathic scoliosis. The findings suggest that melatonin deficiency plays a role in the prognosis of idiopathic scoliosis. Therefore, melatonin supplements may prevent the progression of scoliosis, especially in mild cases with less than a 35º curve [149].

Melatonin and cancer: Physiological and pharmacological blood concentrations of melatonin inhibit tumorigenesis in a variety of in vivo and in vitro experimental models of neoplasia. Evidence indicates that melatonin's anticancer effects are exerted via inhibition of cell proliferation and a stimulation of differentiation and apoptosis. A new mechanism by which physiological and pharmacological blood levels of melatonin inhibit cancer growth *in vivo* is via a melatonin-induced suppression of tumor linoleic acid (LA) uptake and its metabolism to the important mitogenic signaling molecule 13-hydroxyoctadecadienoic acid (13-HODE).

Melatonin suppresses cAMP formation and inhibits tumor uptake of LA and its metabolism to 13-HODE via a melatonin receptor-mediated mechanism in both tissue-isolated rat hepatoma 7288 CTC and human breast cancer xenografts. It has been postulated that in industrialized societies, light at night, by suppressing melatonin production, poses a new risk for the development of breast cancer and, perhaps, other cancers as well.

In support of this hypothesis, light during darkness suppresses nocturnal melatonin production and stimulates the LA metabolism and growth of rat hepatoma and human breast cancer xenografts. Nocturnal dietary supplementation with melatonin, at levels contained in a melatonin-rich diet, inhibits rat hepatoma growth via the mechanisms described above. The nocturnal melatonin signal organizes tumor metabolism and growth within circadian time structure that can be further reinforced by

appropriately timed melatonin supplementation. Dietary melatonin supplementation working in concert with the endogenous melatonin signal has the potential to be a new preventive/therapeutic strategy to optimize the host/cancer balance in favor of host survival and quality of life [150].

However, melatonin could not induce major biochemical changes indicative of a strong anticachectic effect. Nonetheless, the interventions used may have produced a weight-stabilizing effect [151].

Melatonin also produced promising results in patients with cervical cancer; but future research needs to assess the efficacy and safety of melatonin supplement in this specific cancer population [152]. Beneficial effects of melatonin have also been evaluated in breast cancer. Breast cancer diagnoses have peaks in spring and fall, with the authors suggesting that vitamin D in summer and melatonin in winter reduce the breast tumor growth rate in those seasons [153, 154].

Both physiological and pharmacological levels of the pineal hormone melatonin exhibit substantial anticancer activity in tissue-isolated rat hepatoma 7288CTC via melatonin receptor-mediated blockade of tumor uptake of linoleic acid (LA) and its metabolism to the mitogenic signaling molecule 13-hydroxyoctadecadienoic acid (13-HODE) [155]. Role of melatonin has also been proposed for alleviating the toxicity of anticancer chemotherapy and preventing heart failure [156]. However, melatonin requires placebo-controlled trials before recommendations on clinical use for muscle wasting and cachexia [157].

Melatonin and immunity: Melatonin and/or Zn supplementation may activate cellular immunity by stimulating CD4+ and CD8+ production in infected rats with *Toxoplasma gondii* [158]. Melatonin is known to activate T helper cells by means of direct binding to melatonin receptors on both Th1 and Th2 cells. The selective, positive influences of in vivo administered, exogenous melatonin on cells mediating non-specific immunity suggest a plausible mechanism for numerous claims that it is responsible for tumor amelioration in patients [159]. Another experiment was performed to determine the effect of melatonin supplementation on the ontogeny of immunity in the Large White turkey poult. Melatonin administration accelerated the development of cell-mediated (PHA-P-induced CBH reaction) and humoral (CRBC-induced antibody titer) immune responses. The bursal weight, but not thymus or spleen, and body weight were elevated in melatonin treated poults as compared to controls. These data suggest that posthatch melatonin supplementation is beneficial to neonatal immune parameters and growth responses of Large White turkey poults [160].

Melatonin modulates the expression of a number of genes related to inflammation and immunity. Declining levels of melatonin with age may thus relate to some of the changes in immune function that occur with age. Melatonin treatment affects a major shift in the response of the CNS to an inflammatory challenge, causing a transition to a more youthful mRNA expression profile [161]. Many studies have identified a regulatory role for melatonin in the immune system [162].

In aged mice, melatonin treatment can rejuvenate the involuted thymus and partially restore peripheral immune functions [163]. A greater proportion of old mice than of young succumb to an *i.p.* injection of LPS [164]. Melatonin also increases the survival rate of young mice injected with an otherwise lethal dose of LPS [165]. The age-related decline in amplitude of circadian melatonin secretion is especially pronounced in aged demented subjects and the decline of its nocturnal peak is correlated with the severity of cognitive impairment [166].

The biological activity of melatonin is brought about in part by two high affinity G protein coupled receptors (GPCRs) Mtnr1a and Mtnr1b, by quinone 2 NAD(P)H dehydrogenase (NQO2), and by nuclear receptors RZR/ROR. Inflammatory cytokine expression is also modulated by melatonin; for example, Il-2 production by Jurkat cells from human leukemia, is enhanced by way of a nuclear receptor-mediated mechanism [167]. Melatonin also reduces IL-6 secretion in amyloid β peptide-treated brain slices, in a concentration dependent manner [168].

Inflammatory processes in the CNS are increased with normal aging [169], and elevated astroglial activation in aging in mouse brain is evidenced by increased transcription of GFAP [170].

In addition rat microglia also increase basal gene expression of IL-1α, IL-1β and IL-6 cytokines with aging [171]. We have previously reported the influence of low doses of melatonin in mouse brain on the effect of LPS upon genes relating to immune function [172, 173]. The current study examined the global changes of cortical gene expression after acute LPS treatment following extended administration of dietary melatonin. Conditional tree analysis demonstrated that melatonin had significant but minor effects on gene expression in the unchallenged old mice.

However melatonin-treated old animals responded to an LPS challenge in a manner resembling the corresponding response in young rather than that of old mice receiving basal diet. Thus melatonin treatment effected a major shift in the response of the CNS to the inflammatory challenge of LPS in a direction which was closer to the corresponding response of younger animals.

Melatonin and diabetes: Melatonin, a potent antioxidant agent, is essential for glucose homeostasis and regulation. The effect of melatonin on blood glucose level has been studied in both experimental designs and human trials. The effect of orally supplemented melatonin at 1 mg/kg bw for 4 weeks on feeding behavior of non-diabetic and diabetic male Wistar rats has been studied by computerized meal pattern analysis. The notorious metabolic changes occurring in the streptozotocin-diabetic rat can overcome most of the underlying effects of MT supplementation. The possible usage for therapeutic purposes could benefit from the lack of behavioral alterations in diabetic animals [174].

Melatonin supplementation can also have a protective effect on liver glycogen reserves in rats subjected to acute swimming exercise [175]. Data suggest that STZ (streptozotocin) induced hyperglycemia and compounds that act as scavengers of free radicals and peroxynitrite like melatonin may exert protection against STZ-induced toxicity [176].

Another study aimed to examine the effects of melatonin supplementation on liver glycogen levels in rats with streptozotocin-induced diabetes and subjected to acute swimming exercise. The study indicated that melatonin supplementation maintains the liver glycogen levels that decrease in acute swimming exercise, while induced diabetes prevented this maintenance effect in rats [177].

The use of nutritional supplements by patients with type 2 diabetes is estimated at somewhere between 8% and 49%. Melatonin as nutritional supplements was identified as potentially beneficial for type 2 diabetes treatment or prevention. Health providers should investigate drug-nutritional supplement interactions prior to treatment [178]. Another study was conducted to determine the influence of melatonin supplementation on the oxidative stress parameters in elderly NIDDM patients. Findings indicated improvement of antioxidative defense after melatonin supplementation in the NIDDM individuals and suggested melatonin supplementation as an additional treatment for the control of diabetic complications [179].

Melatonin and obesity: Melatonin induces satiety/satiation through several mechanisms. Antioxidant suppression of leptin release and Th1-type activity is beneficial to increase melatonin levels [180]. Both melatonin and leptin show a circadian variation in circulating levels and participate in energy metabolism. Melatonin-supplemented mice had significantly higher plasma leptin levels than control mice. However, melatonin incubation did not cause any marked changes in the amount of leptin secreted from adipose tissue fragments. Nevertheless, melatonin could still influence leptinemia indirectly via regulatory effects in intact animals [181]. However, suspicion is cast upon of dietary supplements including melatonin as potential obesity promoting triggers [182].

Melatonin and blood pressure: Several findings, both from experimental works and clinical studies, support a link between melatonin and BP [183]. In an experimental set up, the role of melatonin supplementation was evaluated in prevention of hypertension in rats with metabolic syndrome. The BP rise was associated with a significant decrease in melatonin secretion during sleep and melatonin administration prevented the rise in BP [184].

In a clinical study, the safety and effects of melatonin treatment were assessed in patients with CAD and impaired circadian pattern of BP. Melatonin supplementation improved circadian pattern of BP in one third (30,8%) of study group

[185]. People with coronary artery disease have reduced serum melatonin levels [186], and diurnal variation in endothelium dependent vasodilation is impaired in these patients [187]. Some preliminary evidence supports the potential use of melatonin in hypertension.

A randomized, double-blind cross-over study found modest but significant lowering of mean BP by melatonin (3 mg/day nightly for 3 weeks) in comparison with placebo in patients receiving angiotensin-converting enzyme inhibitors. The number of patients demonstrating a nocturnal BP-drop rose from 39% to 84% [188]. In another double-blind crossover study, people with untreated hypertension each received 2.5 mg of melatonin or placebo for 3 weeks. Patients experienced a significant drop in BP after 3 weeks of melatonin use. There was also a non-significant trend to greater diurnal BP variation. While there have been no reported adverse events associated with use of melatonin, caution was warranted in patients taking antihypertensive medication [189].

Negative findings were also reported. In a study, melatonin raised BP in 47 patients taking nifedipine [190]. Another study reported reduction of melatonin levels in 42 patients following 10 weeks of β-blocker therapy [191].

Melatonin and exercise: A randomized, double-blind, controlled study investigated the effects of a heavy resistance exercise session (RES) with the oral daytime ingestion of melatonin on the physiological responses and acute performance. The present findings give evidence that oral ingestion of melatonin (6 mg) during daytime with heavy resistance exercise may slightly decrease GH concentrations.

On the other hand, it seems that melatonin administration during daytime does not have any acute (1-2 h) effects either on the maximal jumping ability or on the maximal strength [192]. Another experimental work on rats showed improvement in lipid profile and exercise ability following supplementation with melatonin [193].

Melatonin and GERD: Melatonin administration has been shown to protect against esophageal lesions in animals. Moreover, in a randomized, single-blind clinical trial of subjects with gastroesophageal reflux disease (GERD), the combination of melatonin with other natural supplements was found to be superior to omeprazole, a proton pump inhibitor (PPI) [194].

In another single blind, randomized study, another combination of melatonin and other natural supplements was compared with omeprazole and was found to help patients with GERD. Melatonin had known inhibitory activities on gastric acid secretion and nitric oxide biosynthesis.

Nitric oxide had an important role in the transient lower esophageal sphincter relaxation (TLESR), which was a major mechanism of reflux in patients with GERD. This formulation promoted regression of GERD symptoms with no significant side effects [195].

Melatonin and IBS: Inflammation and oxidative process are associated with inflammatory bowel disease (IBD). Regarding anti-inflammatory and antioxidant potentials, melatonin has been found beneficial in several experimental and clinical studies including inflammatory bowel disease (IBD). Three clinical trials and fifteen non-clinical studies were conducted to study the efficacy of melatonin in IBD. The majority of these studies indicate that melatonin has a positive impact on IBD with no or negligible side effects.

Such results have been mostly explained through free radical scavenging and diminishing inflammation. It is yet crucial to determine the efficacy of melatonin in combination with other established drugs in more clinical trials, not only for further confirmation of its efficacy, but also to investigate its possible side effects in longer durations of therapy [196].

Melatonin in peri-operative use: Perioperatively, melatonin has been used as a premedicant, sedative and analgesic. It decreases paediatric emergence delirium. The antioxidant properties of melatonin are being investigated for use in sepsis and reperfusion injuries.

It would appear that patients on melatonin supplements should continue taking them perioperatively because there may be benefits. Melatonin and its analogues will be increasingly encountered in the perioperative setting [197].

Melatonin and reproductive system: Several roles of melatonin have been identified both in experimental models and human clinical studies. Melatonin may negate the consequences of IUGR during specific abnormalities in umbilical blood flow as long as sufficient uterine blood perfusion is maintained during pregnancy [198]. Melatonin has also been shown to exert beneficial effects on fertility, pregnancy wellness and embryo development, whose requirements increase during pregnancy [199]. Associations have been reported between hormonal factors and melanoma; melatonin inhibition increases the risk of melanoma by increasing circulating oestrogen levels [200].

Evidence is also present that this indoleamine is involved in pre- and postnatal brain (and ocular) development and intrauterine growth. In the absence of maternal melatonin, short gestation infants have a prolonged period of melatonin deficiency. Melatonin supplementation, which has a benign safety profile, may help reduce complications in the neonatal period that are associated with short gestation. This treatment might result in a wide range of health benefits, improved quality of life and reduced healthcare costs [201].

The effects of pinealectomy on the progression of endometriosis explants were reversed by melatonin [202]. One study examined the effects of melatonin and level of nutrition on embryo yield during anestrous and breeding season. Undernutrition impaired the viability of sheep embryos in the reproductive season, particularly among ewes that were given melatonin supplements subcutaneously, but melatonin appeared to improve embryo quality in the AS, which suggests that the mechanisms involved in the interactive effects of melatonin and nutrition on embryo development are influenced by season [203].

Another study aimed to investigate the effect of estradiol and progesterone and melatonin supplementation on TNF-alpha levels in ovariectomized and pinealectomized rats. Melatonin reduced TNF-alpha levels in ovariectomized rats [204]. Melatonin was tested in an experiment to determine if hair re-growth in dogs with hair cycle arrest (alopecia X) was associated with a decrease in follicular oestrogen receptors. Hair re-growth was not associated with a change in oestrogen receptor-alpha staining. Melanin aggregates within basal cells and hair were an occasional finding [205]. Melatonin implantation allowed a high ovulation rate [206, 207] and and a large number of healthy cleaved oocytes and blastocyst rate are obtained [208, 209].

Melatonin regulated seasonal reproduction through changes in the pulsatile secretion of GNRH and LH [210, 211]. Its action on the activity of GNRH neurones appeared to be indirect. A number of studies have suggested that different neurotransmitters are involved in the regulation of LH secretion by melatonin or photoperiod, especially in ewes [212-215].

The neuroendocrine mechanism downstream of the action of melatonin, leading to the regulation of LH secretion, appears to involve several dopaminergic structures in the hypothalamus, such as the A14 and A15 nuclei of the lateral retrochiasmatic area [216] and the arcuate nucleus–median eminence region [217]. However, the information available on the effect of neuro-excitatory amino acid receptors in LH secretion in melatonin-implanted goats, or goats subjected to different levels of nutrition, is lacking [218].

The melatonin implantation by nutrition interaction had a significant effect on LH secretion. To our knowledge, this is the first report of such an observation in goats. However, in sheep, this interaction [219], and the BCS by melatonin implantation interaction have been reported to affect ovulation rate [220]. All these authors report the enhancing effect of melatonin implantation on the ovulation rate to be more pronounced in ewes with a low, rather than a high, feed intake. The practical implications of this interaction could be important in induced reproductive activity during seasonal anoestrus in goats that have suffered reduced food availability.

Melatonin and tinnitus: Improvements in tinnitus have been noted in patients taking melatonin for significant sleep disturbances [221]. A recent, randomized, double-blind, placebo-controlled study found that melatonin reduced subjective ratings of tinnitus, tinnitus visual analog scale scores and tinnitus loudness more than placebo; these improvements were substantially larger if melatonin was combined with the antipsychotic sulpiride, a selective dopamine D_2 antagonist [222-224].

Melatonin has been found to protect against noise- and drug-induced hearing loss [225, 226]. Because sleep disturbances represent a major complaint and complicating factor in tinnitus, melatonin was evaluated as a treatment for tinnitus in clinical studies.

In a double-blind, placebo-controlled, crossover study, scores of tinnitus severity improved by approximately the same degree with melatonin and placebo. There was a trend toward improved sleep scores with melatonin, but the effect was not statistically significant [227]. A subsequent open label study found statistically significant improvements with melatonin treatment; however, it is difficult to evaluate the significance of these findings because of the lack of a placebo control group and moderate effect size [228].

Miscellaneous: The dietary supplement of melatonin had no effect on the impression hardness or the concentrations of cysteine and methionine in samples of claw horn collected from a range of sites, or on the areas of erosion in the sole and heel [229]. The effects of dietary melatonin supplementation were tested on performance, carcass characteristics, and excretion of nitrogen and some minerals in broiler Japanese quails exposed to high-ambient-temperature stress (34°C).

No interactions between melatonin and temperature were found in the parameters measured. The results of the study show that melatonin supplementation attenuated the retardation in performance as well as the excretion of minerals caused by heat stress in broiler quails. So, melatonin might offer protection against heat-stress-related depression in the performance of broiler quails [230].

The effect of chronic melatonin treatment or pineal grafting (PG) was evaluated in old mice on the apoptosis of both thymocytes and spleen lymphocytes under conditions of either serum deprivation or glucocorticoid or zinc administration. The apoptosis was correlated with the modulation of thymus and adrenal weight and corticosterone and zinc plasma levels induced by melatonin treatment or PG in old mice. Results suggest that MEL treatment or PG prevent age-related thymus involution through regulation of thymocyte apoptosis which, in turn, occurs through modulation of the pituitary-adrenal axis and zinc turnover determined by the pineal hormone [231]. Studies have found melatonin useful in cocaine abuse [232], seasonal affective disorder [233, 234], delirium [235], headache [236, 237], gallstone [238, 239], and amyotrophic lateral sclerosis [240]. Few studies have suggested melatonin as an effective radio-protective agent [241-245].

DISCUSSION: Dietary supplements and alternative health care products use and availability have increased during the past decade. Epidemiologic studies suggest that patients turn to dietary supplements because of a reluctance to take prescription medications or a lack of satisfaction with the results. They often perceive dietary supplements to be a safer or more natural alternative. Patients with mental health conditions, including depression, anxiety, and sleep disorders, are among those who use dietary supplements. Agents discussed for use in sleep disorders include melatonin, Familiarity with the evidence for use and the possible resulting risks can help health professionals to guide patient decisions regarding use of dietary supplements [246].

The prevalence of supplement use is largely unknown, but is thought to be widespread. That a product is "natural" does not mean that it is either safe or effective. Many supplements are potent drugs that lack sufficient data on safety, dose-response relationships, drug interactions, and purity [247]. It has been reported that melatonin consumption has resulted in eosinophilia in some humans taking high doses of this supplement.

Although there has not been a major outbreak of eosinophilia from consumption of melatonin, this study clearly suggests that tighter control and regulation of nutritional supplements sold and used as drugs is necessary [248]. Few studies reported some insignificant unwanted effects, though the evidences are conflicting. Substantial benefits from different dietary supplements and nutraceuticals, mostly antioxidant agents has been observed with a high tolerability and safety profile [249].

In particular, a relatively large body of evidence support the use of anti-oxidants including melatonin. However there is a need for data about the long-term safety of a large part of these products. Further clinical research is advisable to identify between the available active nutraceuticals

and those with the best cost-effectiveness and risk-benefit ratio for widespread use in a general population with low added cardiovascular risk related to uncomplicated hypertension. Caution is warranted especially in patients taking pharmacotherapy and individuals with auto-immune disorders [250].

CONCLUSION: Melatonin supplements can be used for insomnia, cancer and complaints of ageing, but cautiously. Its use in diabetes, hypertension, GERD, IBS and other purposes awaits further validation studies.

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