PHYTOMELATONIN FOUND IN EMBRYONIC PLANT EXTRACTS (EPEs) & Protocol for Insomnia and other Sleep Disorders.

by

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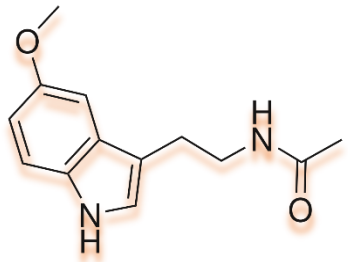
Researching melatonin and phytomelatonin from medicinal plants revealed many new insights and at times even novel pharmacological uses for a fundamentally essential neurohormone that is still not completely understood. I hope that, like for me, this information will further your medical and phytochemistry knowledge.

MELATONIN – PHYTOMELATONIN ($C_{13}H_{16}N_2O_2$) is a neurohormone, also known as Herbatonin and Fitomelatonin. The synthetic analog is ~{*N*}-[2-(5-methoxy-1~{*H*}-indol-3-yl)ethyl]acetamide.



Phytomelatonin

Melatonin – Phytomelatonin (*N*-acetyl-5-methoxy tryptamine) is an indoleamine, a human neurohormone and phytohormone. It is now known that ***phytomelatonin from plants may have functions analogous to those of humans*** and ***animals***.

This is precisely why the timing of the harvest of certain plants is so important, as in the case of phytomelatonin, which is best collected in the evening, when having nocturnal peak concentration of phytomelatonin – just like what is observed in humans: melatonin level being highest at night. Sour Cherries Montmorency – Prunus Cerasus (bud of leaves) is the only embryonic plant harvested late fall, when the longer nights and shorter days increase its phytomelatonin concentration; it should be collected two hours after sunset. St John's Wort – Hypericum Perforatum (bud of flowers), on the other hand, is best harvested in the spring, late at night – between 10-11 pm – when not only phytomelatonin but also all other phytochemicals are found in higher concentration. All of these petite details make a huge difference in peak phytochemical concentration harvesting.

Phytomelatonin level varies greatly from plant to plant, as well as among different tissues/organs of the same plant; moreover, temperature, pH, effects of present metal ions, sensitivity of analytics and extraction methods caused these diversities. Phytomelatonin was found in extremely high concentrations when obtained in green bud of leaves or bud of flowers of the respective plants (total young plants, fresh leaves, or young flowers), and exceptionally high in some embryonic roots. Seeds were frequently found to be another good source of high phytomelatonin, but the concentrations were not that extreme and mostly remained between 1 and 100 ng/g. Phytomelatonin was shown to possess antiaging activity, which significantly decreased after 14 days from

germination; little is found in matured plant tissues, just like what is observed with human aging. The extreme divergence of phytomelatonin levels between species and between plant organs may, on the one hand, appear puzzling, but on the other hand, is clearly indicative of the fact that phytomelatonin cannot have a single function in plants. Not all reports on phytomelatonin levels in photoautotrophs are equally reliable, for methodological reasons. Nevertheless, high amounts found in a number of well-designed studies, also in relation to UV exposure, indicate that the cytoprotective properties known from animals may play a role in plants also (Conti et al., 2002; Hardeland et al., 2007).

In the blood of mammals, melatonin levels exhibit a rhythm with low values ***during the day*** and ***high levels at night***. Since this is common to all mammals regardless of their locomotor activity pattern, ***melatonin has been referred to as the hormone of darkness or the chemical expression of darkness***. This diurnal pattern of fluctuating melatonin levels in animals is perturbed if light exposure occurs at night, while in constant dark conditions the rhythm persists, i.e., the rhythm is truly circadian. Considering the ubiquitous nature of the blood melatonin rhythm in mammals, there was also interest in whether similar variations existed in plants and if phytomelatonin was involved in photoperiodism in these species. Research studies found that in most plant species, nighttime levels of phytomelatonin exceeded those measured in plants harvested during the day.

In 1959, melatonin was detected in humans. For a very long time, it was thought that melatonin occurred only in animals and humans. In 1993, phytomelatonin was also detected in plants (van Tassel & O'Neill, 1993).

For decades, investigations concerning occurrence of melatonin in different body parts revealed that ***significantly high concentrations are found in the bile fluid***, ***bone marrow***, ***cerebrospinal fluid***, ***ovary***, ***eyes***, ***lymphocytes, very prominent in the skin*** and is ***differentially distributed in subcellular organelles***. It was reported that ***melatonin levels in organs*** mentioned above ***may be 10- to 1000-fold higher than in the plasma***. ***High concentrations of melatonin across different organs*** suggest a ubiquitous, ***biologically highly relevant existence of tissue-specific***, ***local melatoninergic systems,*** which ***have the biological role of counteracting specific tissue-related regional stressors exactly at the place where they occur***. ***In the skin***, ***a melatoninergic antioxidative system (MAS) has been recently discovered*** in a ***highly differentiated manner regulating skin homeostasis*** and—very importantly—having the potential to ***prevent the harmful consequences of UV solar skin damage***, i.e., skin aging and even skin melanoma cancer and others (Kleszczynski & Fischer, 2012).

Functional activity of serotoninergic and melatoninergic systems are expressed in the skin: Expression of membrane receptors for melatonin regarding tissue and cell type are found in MT1 and MT2 proteins. Melatonin receptors are found in the whole brain tissue, pituitary, adrenal glands, normal skin, basal cell carcinoma epidermal keratinocytes, hair follicles keratinocytes and melanocytes, neonatal keratinocytes, HaCaT keratinocytes, epidermal melanocytes dermal fibroblasts, and hair follicles papilla fibroblasts, as well as epidermis (Stratum granulosum and spinosum), eccrine glands, blood vessels endothelium, and upper outer root sheath and inner root sheath of hair follicles. The nuclear retinoid-related orphan receptor α (RORα) contains at least four splicing variants:

RORα1, RORα2, RORα3, and RZRα (RORα4). All of the tested skin cells expressed at least one of three RORα isoforms while RORα3 was consistently absent (Slominski et al., 2003).

The ubiquitous presence and high concentrations of melatonin in higher plants, as opposed to animals, led to introduction of the term “phytomelatonin” in 2004. At present, phytomelatonin has been shown to induce antioxidant, antistress, and growth-promoting effects (Shibaeva et al., 2018). ***Phytomelatonin is an adaptogen***.

The levels of phytomelatonin are determined by cyclodextrin-modified micellar electro-kinetic chromatography, enzyme-linked immuno sorbent assay, radioimmunoassay, high performance liquid chromatography, liquid chromatography with electrochemical detection, liquid chromatography with fluorometric detection, liquid chromatography-mass spectrometry, and liquid chromatography-ultraviolet spectrophotometry. Phytomelatonin has roles in plants similar to those of animals that protect plants against extreme conditions such as temperature change, UV exposure, environmental pollution, toxins, drought oxidative and (a) biotic stress. Phytomelatonin plays an important role to maintain the vitality of the plants. Smoking cigarettes, drinking alcohol, excessive coffee consumption, some medications and disorders ***are known to suppress the production of melatonin in the body*** (Koca et al., 2017).

Although the biochemical pathways and enzymatic mechanisms of phytomelatonin formation have yet to be fully explored, studies using radioisotope tracer techniques indicate that, in higher plants, tryptophan is the common precursor for both serotonin and melatonin as well as for indole-3-acetic acid (IAA), (Murch et al., 2000). In plants, evidence also indicated involvement of phytomelatonin in chlorophyll preservation, thereby promoting photosynthesis (Kolar & Machackova, 2005; Van et al., 1995).

In plants, the phytohormone auxin, ***indolyl-3-acetic acid (IAA***), ***bears some resemblance to melatonin since both are indole compounds*** and have a common biosynthetic pathway through the compound tryptamine in the tryptophan-dependent IAA biosynthetic pathway (Arnao, 2014).

Indole-3-Propionic Acid (IPA) is another phytohormone and a melatonin-related molecule shown to protect hepatic microsomal membranes from iron-induced oxidative damage: relevance to cancer reduction (Karbownik et al., 2001).

The biosynthesis of ***melatonin/phytomelatonin*** occurs through hydroxylation, decarboxylation, acetylation, and a methylation starting with L-tryptophan. L-tryptophan is produced in the shikimate pathway from chorismate or is acquired from protein catabolism. First, L-tryptophan is hydroxylated on the indole ring by tryptophan hydroxylase to produce 5-hydroxytryptophan. This intermediate (5-HTP) is decarboxylated by pyridoxal phosphate and 5-hydroxytryptophan decarboxylase to produce serotonin. Serotonin is itself an important neurotransmitter, but is also converted into *N*-acetylserotonin by serotonin *N*-acetyltransferase and acetyl-CoA. Hydroxyindole *O*-methyltransferase and *S*-adenosyl methionine convert *N*-acetylserotonin into melatonin through methylation of the hydroxyl group (Bochkov et al., 2012; Hardeland, 2015; Tan et al., 2013; Tordjman et al., 2017).

HUMANS	PLANTS
Tryptophan	Tryptophan
↓ Tryptophan hydroxylase	↓ Tryptophan decarboxylase
5-Hydroxytryptophan	Tryptamine
↓ 5-Hydroxytryptophan decarboxylase	↓ Tryptamine hydroxylase
5-Hydroxytryptamine (Serotonin)	5-Hydroxytryptamine (Serotonin)
↓ *N*-Acetyltransferase	↓ *N*-Acetyltransferase
N-Acetylserotonin	*N*-Acetylserotonin
↓ Acetylserotonin methyltransferase	↓ Acetylserotonin methyltransferase
Melatonin	**Phytomelatonin**

***Phytomelatonin* was seen to have double the antioxidant activity** of ascorbic acid or trolox and approximately double that of other indoles such as indolyl-3-acetic acid, indole-3-methanol, indole-3-propionic acid, indole-3-butyric acid, and tryptophan (Arnao, 2014).

Melatonin in Plants – Focus on a Vertebrate Night Hormone with Cytoprotective Properties. Although the presence of melatonin in plants may be attractive from a nutritional, nutraceutical, or medicinal point of view, the potential roles of this compound in plant physiology are, perhaps, equally or even more exciting. However, ***melatonin should no longer be exclusively seen as a molecule mediating dark signals***, but its other ***recently discovered broad actions as a metabolic modulator***, e.g., of ***mitochondrial functions*** should come into focus (Hardeland et al., 2007).

Loss of mitochondrial function is a fundamental contributor to aging in every cell, tissue, organ, and body system in humans. ***The process of aging is considered tightly related to mitochondrial dysfunction***. One of the causes of aging is an ***increased sensitivity to the induction of mitochondrial permeability transition pore (mPTP) opening in the inner membrane of mitochondria***. The role of melatonin whose level decreases with aging is well understood. The present study demonstrated that long-term treatment of aged rats with ***melatonin improved the functional state of mitochondria***; thus, ***the Ca^{2+} capacity was enhanced***, and ***mitochondrial swelling was deaccelerated in mitochondria***. ***Melatonin prevented mPTP*** and ***impaired the release of cytochrome c*** and ***2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase)*** from mitochondria of both young and aged rats. This study data suggest that ***melatonin retains CNPase inside mitochondria***, ***thereby providing protection of the protein against deleterious effects of 2',3'-cAMP in aging*** (Baburina et al., 2017).

Mitochondria are Energy Power Producers

An enormous contributor to mitochondrial dysfunction is the opening of a hole in the mitochondrial inner membrane that decreases their ability to produce energy. ***Preventing or closing this hole is a key to preserving youthful mitochondrial function***. Until just recently, there were no drugs able to do so ***permanently the way melatonin augmentation can***.

Cells are the basic components of all living organisms. The two major types are prokaryotic and eukaryotic cells. Eukaryotic cells have membrane-bound organelles that perform essential cell functions. Mitochondria are considered the "powerhouses" of eukaryotic cells. These organelles generate power by converting energy into forms that can be used by the cell. Located in the cytoplasm, mitochondria are the sites of cellular respiration. Cellular respiration is a process that ultimately generates fuel for the cell's functions and functions from the foods we consume. Mitochondria produce the energy required to perform cell mitosis (division), growth, and death (apoptosis).

Mitochondria have a distinctive oblong or oval shape and are bounded by a double membrane. The inner membrane is folded, creating structures known as cristae. Mitochondria are found in both mammals and plant cells. They are found in all body cell types, except for mature red blood cells (RBCs), which contain no mitochondria. The number of mitochondria within a cell varies depending on the type and function of the cell. The absence of mitochondria and other organelles in RBCs leaves room for the millions of hemoglobin molecules needed ***in order to transport oxygen throughout the body***. Muscle cells, on the other hand, may contain thousands of mitochondria required to provide energy for muscle activity. Mitochondria are also abundant in fat cells and liver cells.

MELATONIN FOR MITOCHONDRIA HOMEOSTASIS

- Alleviate fatty liver disease, protecting the liver mitochondria (Zhou et al., 2017).
- Inhibit cardiolipin peroxidation in mitochondria and prevent the mitochondrial permeability transition and cytochrome c release.
- Support the CNPase enzyme, and the resulting prevention of mitochondrial permeability transition pore (mPTP) holes formation. CNPase levels decrease by 34% with aging, accompanied with loss of mitochondrial electrical function by up to 69% (Baburina et al., 2017).
- Extend lifespan and prevent age-associated disease from insects to mammals by protecting the mitochondria,
- Reduce endoplasmic reticulum stress and preserve sirtuin 1 (SIRT1) expression in neuronal cells after hypoxia–ischemia (Carloni et al., 2014).
- Regulate aging and neurodegeneration through energy metabolism, epigenetics, autophagy, and circadian rhythm pathways.
- Are the powerhouses of our cells. By “burning” fuel supplied by the food we eat, mitochondria release massive amounts of energy needed to power the human body.
- Prevent age-related mitochondrial dysfunction in the brain cells and prevent neurodegeneration.
- Prevent apoptosis of musculo skeletal cells by increasing mitochondrial energy production.
- Protect the heart muscle cells following loss of blood flow from acute or post ischemia.
- The highest concentrations of melatonin are found inside the mitochondria cells, which suggests an important role on energy currency production and cellular integrity.

- Phytomelatonin and melatonin increase adenosine triphosphate (ATP). ATP drives every cellular function that requires energy in the body. Low levels of ATP can lead to poor tissue, organ, and system function throughout the body.

Recently a study demonstrated that the protection against oxidative stress by melatonin could directly contribute to the maintenance of telomeres in aging mouse ovaries. Mice treated with melatonin significantly decreased mitochondrial reactive oxygen species (ROS) production. **Telomeres erode rapidly in response to oxidative stress**. Ovaries from mice treated with melatonin for 12 months had ***longer telomeres*** than those from age-matched mice without treatment. Telomerase activity in mice treated with melatonin for 12 months was higher than in age-matched untreated mice. Aged mice treated with melatonin for 12 months had markedly reduced 8-OHdG level in mitochondria compared with those of age-matched untreated mice. Long-term treatment with melatonin prevented aging-associated oxidative stress in the ovarian mitochondria, ***as assessed by the recovery of GSH levels*** and GSH/GSSG ratios (Song et al., 2016).

Melatonin is a molecule with a ***wide variety of interesting functions*** in humans. This neuro-endocrine hormone has been studied for ***use in antitumor treatments of various kinds***. Melatonin seems to play ***an important role in multiple stages of tumor development***, ***both in growth/proliferation*** and in ***apoptosis*** and ***metastasis***, and through ***immunological regulation***. While synthetic melatonin is usually used in these studies, ***this work looks at an alternative*** source of ***melatonin from plant origin called phytomelatonin***. ***Apoptosis is the main response to high phytomelatonin doses in some cancer cell types***. Interest in this proposal ***arose from the need to avoid the unwanted byproducts present in synthetic melatonin preparations***. The substitution of synthetic melatonin by phytomelatonin in medical treatments ***could also lead to substantial improvements in the results***. The application of phytomelatonin in clinical studies is proposed as an objective (Arnao & Hernández-Ruiz, 2018).

The use of phytomelatonin from plants versus from synthetic or animal source melatonin

Melatonin and phytomelatonin ***are the same molecule***, “melatonin” referring to melatonin of synthetic or animal origin and ***“phytomelatonin” to that of plant origin***. Previously, melatonin was obtained from animal sources such as cows, but due to the risk of viral infection, synthetic production is often preferred, using a simple and very productive process (Hugel & Kennaway, 1995; Prabhakar et al., 1999; Thomson et al., 2003). Phytomelatonin from plant is once again proven to be a superior source of this hormone for human use and possess more therapeutic benefits than from any other source. In addition, phytomelatonin ***is more readily capable of crossing the brain blood barrier***.

Since the discovery of melatonin in 1958 by Lerner and coworkers (Lerner et al., 1958), the organic synthesis of melatonin has been significantly improved with the arrival of more productive and economic processes. Synthetic melatonin is generated with yields of over 80%, although many byproducts, i.e., ***unwanted compounds side effects of the chemical melatonin*** preparation processes, also appear. The list below shows some of the most common of these present in the commercially available ***synthetic melatonin preparations***. ***Most occur at concentrations below 0.5%***, although it is difficult to establish the exact concentration due to the different methods and mother materials from which the synthetic melatonin is obtained. These contaminants can be classified

according to the synthetic route used (Naylor et al., 1999; Williamson et al., 1997). Thus, ***in "classic" organic melatonin synthesis from derived-indoles (methoxyindoles, etc.)***, ***the contaminants are related to tryptophan***, which have also been described in tryptophan supplements. Other contaminants, such as ***oxidized forms of melatonin*** or ***condensation-related products***, ***arise from the instability of melatonin***. In other cases, ***up to 14 contaminants have been described in the organic synthesis of melatonin from phthalimide*** (Arnao & Hernández-Ruiz, 2018).

Common unwanted byproducts from synthetic melatonin preparations include:

1. 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
2. 3-(phenylamino)alanine (PAA)
3. 1,1′-ethylidenebis-(tryptophan) (so-called peak E)
4. 2-(3-indolylmethyl)-tryptophan
5. formaldehyde-melatonin
6. formaldehyde-melatonin condensation products
7. 5-hydroxy-tryptamine derivatives
8. 5-methoxy-tryptamine derivatives
9. *N*-acetyl- and diacetyl-indole derivatives
10. 1,3-diphthalimidopropane
11. hydroxy-bromo-propylphthalimide
12. Chloropropylphthalimide

Other contaminants, such as ***oxidized forms of melatonin*** or condensation-related products, arise ***from the instability of melatonin from synthetic*** or ***animal source***. The presence of ***solvent residues*** due to extraction protocols is also common. Furthermore, a plant source of ***phytomelatonin used must be controlled*** to ***avoid the presence of pesticides or other compounds due to previous cultivation*** or ***postharvest treatments***. The use of ***wild or organically grown plants as sources of phytomelatonin*** should prevent the presence of undesirable chemicals in supplements.

The use of phytomelatonin in dietary supplements and in other applications such as cosmetics should be considered, although very few products formulated with phytomelatonin exist commercially. Also, its use as an ***antitumoral effector*** may be interesting since it would prevent residual synthetic byproducts from being incorporated during tumor treatments. Also, ***the presence in the phytomelatonin-rich extracts of several plant antioxidants such as ascorbic acid***, ***simple phenols***, ***flavonoids***, ***carotenoids***, ***tocopherols, among others***, ***might be relevant for maintaining an appropriate redox balance***. Some phytomelatonin-rich foods have been checked in experimental tests, all showing, in general, ***healthy effects such as increases in plasma melatonin levels*** and ***antioxidant status***. Also, ***an increase in sleep quality parameters has been observed*** (Maldonado et al., 2009; Reiter et al., 2005).

In humans, melatonin/phytomelatonin is a full agonist of melatonin receptor 1 (picomolar binding affinity) and melatonin receptor 2 (nanomolar binding affinity), both of which belong to the class of G-protein coupled receptors (GPCRs). Melatonin receptors 1 and 2 are both Gi/o-coupled GPCRs, although melatonin receptor 1 is also Gq-coupled. Melatonin also acts as a high-capacity free radical scavenger within the mitochondria, which also promotes ***the expression of antioxidant enzymes such as superoxide dismutase***, ***glutathione peroxidase***, ***glutathione reductase***, and ***catalase*** *via* its signal transduction through melatonin receptors. The oral intake of phytomelatonin-rich plants

produces an ***up to 4-fold increase in basal melatonin levels in the bloodstream***. This ***increase occurs 60–120 min after the consumption of phytomelatonin-rich plants***. In the case of walnuts, a correlated increase in antioxidant activity in the blood was observed, indicating that phytomelatonin (and also other phytochemicals) ***improved*** and ***increased the antioxidant pool***. Among other roles, melatonin plays an important part in the regulation of sleep, body temperature, the state of alertness and the degree of concentration or performance, and cortisol rhythms. Melatonin is a sleep initiator for opening the circadian sleep-gate, ***acting as a sleep regulator***. Melatonin adjusts the timing or ***reinforces oscillators of the central biological clock***. Exogenous melatonin administration alters the timing of bodily rhythms, including sleep, where phase delays are observed with the morning administration of melatonin, while phase advances are found after evening administration (Lewy et al., 1992).

Many sleep disorders have been treated with melatonin: delayed sleep phase syndrome, night shift-work sleep disorder, seasonal affective disorder (SAD), sleep disorders in the blind and aging, and in pathophysiological disorders of children, with notable improvements in the 'sleep quality.' The most widespread disorder treated with melatonin is jet-lag, a de-phasing of the sleep-wake rhythms resulting from trans-oceanic flights.

Phytomelatonin ***has a different biosynthetic pathway than*** ***melatonin***. In particular, ***it has more alternative routes of synthesis reflecting a greater capacity to adapt to metabolic changes***. Briefly, three different principal ways have been described: Tryptophan is converted into tryptamine by the enzyme tryptophan decarboxylase (TDC), and then Tryptamine, by tryptamine 5-hydroxylase (T5H), is catalyzed to serotonin. Serotonin *via* *N*-acetylation, mediated by the enzyme serotonin *N*-acetyltransferase (SNAT), is converted in *N*-acetylserotonin that is methylated by acetylserotonin methyl transferase (ASMT), which generates phytomelatonin. Another enzyme, caffeic acid *O*-methyltransferase (COMT), could also mediate methylation of *N*-acetylserotonin in plants (Byeon et al., 2014). Serotonin may also be converted into 5-methoxytryptamine by ASMT or COMT and finally generate phytomelatonin *via* SNAT activity. Moreover, phytomelatonin could be generated from tryptamine by formation of *N*-acetyltryptamine by a pathway mediated by SNAT. *N*-acetyltryptamine *via* T5H activity is converted into *N*-acetylserotonin and then using the previous described pathway in melatonin. Finally, phytomelatonin can be generated through the formation of 5-methoxytryptamine (Arnao & Hernández-Ruiz, 2018).

Artificial Light Pollution ***leads to a much-decreased level of melatonin in all mammals***: ***Excessive light exposure during the night is becoming progressively more common throughout the world***, particularly in areas where electricity is commonly used. Also, the availability of artificial light has allowed humans to work or recreate throughout the 24-hour day. Based on photographs taken of the Earth from outer space, it is also apparent that ***true darkness is disappearing rapidly***. ***For years it was assumed that polluting the daily dark period with light was inconsequential in terms of animal/human physiology***. ***That assumption***, ***however***, ***has proven incorrect***. ***Light at night has two major physiological actions***, i.e., it ***disrupts circadian rhythms*** and ***suppresses the production of melatonin by the pineal gland***. Moreover, both these changes are light intensity- and wavelength-dependent. Both human epidemiological and experimental studies on animals have documented that ***a***

potential negative health consequence of chronodisruption and ***nocturnal melatonin inhibition is cancer initiation*** and ***growth***. We only know how many each day are being diagnosed with cancer of all types. In epidemiological studies, ***the frequency of each of the following cancers has been reportedly increased in individuals who routinely work at night or whose circadian rhythms are disrupted for other reasons*** (e.g., due to jet lag): ***breast***, ***prostate***, ***endometrial***, and ***colorectal***. Likewise, in experimental animals, cancer growth is exaggerated when the animals are repeatedly phase advanced (as occurs during easterly flights) or exposed to light at night. A variety of mechanisms have been examined to explain ***how the suppression of melatonin exaggerates cancer risk***. Mechanistically, how chronodisruption (without a consideration of melatonin suppression), would enhance cancer frequency is less clear. In addition to cancer, there may be other diseases that result from the chronic suppression of melatonin by light at night. Further studies are urgently needed in view of these facts (Reiter et al., 2007).

When the International Agency for Research on Cancer (IARC) ***classified shift-work that involves circadian disruption as probably carcinogenic to humans in 2007***, this was the prelude to extensive experimental and epidemiological research in coming years. Indeed, with some 20% of people worldwide being engaged in some type of work at unusual times, including the night, ***it is a must to investigate***, and ***to clarify as soon as possible***, ***the biologically plausible links via circadian disruption with epidemic cancers such as of the breast or prostate***. Surprisingly, neither the IARC information available so far nor the general literature provides a clear definition of what the critical component in the postulated chain of causation, namely circadian disruption, is. ***Here is offered a definition for chronodisruption (CD)***, a concept which these researchers proposed in 2003 and which was operationalized recently in research, that addressed ***the putative links between shift-work, time-zone-travel,*** and ***human cancers independently of the IARC*** and ***led to similar causal interpretations***. As a basis for further research in this area with possible high relevance for public health, they: (i) elaborate the definition of CD, ***with melatonin being a key biological intermediary***, by putting critical disruptions, and the resulting disorder, of circadian clocks, biological rhythms and circadian organization into thematic and historical context with Colin Pittendrigh's insights almost half a century ago; (ii) provide material on what chronodisruptors are; and (iii) pose a key question that needs to be answered by and for experimental and epidemiological CD research. This is in hope that defining CD can contribute to studies that may help to find clues to a background incidence of epidemic internal cancers for which so far, many cases lack causal explanations (Erren & Reiter, 2009).

Obesity and **metabolic syndrome**: ***association with chronodisruption***, sleep deprivation, and melatonin suppression. Obesity has become an epidemic in industrialized and developing countries. In 30 years, unless serious changes are made, a majority of adults and many children will be classified as overweight or obese. Whereas fatness alone endangers physiological performance of even simple tasks, the associated co-morbidity of obesity including metabolic syndrome in all its manifestations is a far more critical problem. If the current trend continues as predicted, health care systems may be incapable of handling the myriad obesity-related diseases. The financial costs, including those due to medical procedures, absenteeism from work, and reduced economic

productivity, will jeopardize the financial well-being of industries. The current review summarizes the potential contributions of three processes that may be contributing to humans becoming progressively more overweight: circadian or chronodisruption, sleep deficiency, and melatonin suppression. Based on the information provided in this survey, lifestyle factors (independent of the availability of abundant calorie-rich foods) may aggravate weight gain. ***Both epidemiological*** *and* ***experimental data support associations between disrupted physiological rhythms***, ***a reduction in adequate sleep***, and ***light-at-night-induced suppression of an essential endogenously produced molecule, melatonin***. The implication is that if these problems were corrected with lifestyle changes, body weight could possibly be more easily controlled (Reiter et al., 2012).

Taking melatonin or phytomelatonin at the right time can help you shift more quickly to a new time zone, but the right light exposure at the right time is also an effective method if you are trying to eliminate jet lag.

Melatonin is known to reduce jet lag, especially, when travelling eastbound. However , if the time it is taken is not correct, it can instead delay adaption (Boutin et al., 2005). Give it enough time to work. Take melatonin 30 to 60 minutes before sleep for eastbound travel; it can also be taken en route, 30 minutes prior to the target bedtime at your destination. It doesn't need to be taken en route for westbound travel.

When to take melatonin or phytomelatonin for jet lag?

- When crossing fewer than five time zones, take melatonin after you arrive at your destination.
- When crossing five or more time zones, take melatonin on the day of your travel.
- When traveling to a time zone where local time is ahead of your time, take melatonin at your expected bedtime in the new time zone.
- Take melatonin 30 minutes to 2 hours before you plan to go to sleep.

Take only the dose you need. A typical dose for melatonin ranges from 0.5 mg to 5 mg. Small doses–as little as 0.5 mg–seem to be just as effective for reducing jet lag symptoms; however, higher doses may be better at promoting sleep. Best is to take phytomelatonin from Sour Cherries Montmorency – Prunus Cerasus (bud of leaves) 50-100 drops into a little filtered water and sip over a period of 5 minutes.

Before you depart for your trip

- If you're traveling for an important event, consider arriving a day or two earlier so that you can properly acclimate to your new time zone.
- Gradually adapt to your new schedule before your departure by going to bed an hour earlier or later than normal each evening, depending on the direction you're traveling.
- Be sure that you're well rested before your travels. ***Being sleep-deprived to begin with can exacerbate jet lag***.

Phytomelatonin is a chelator of excess or toxic **metals**: Al, Cd, Cu, Fe, Pb, and Zn (Limson et al., 1998).

Both melatonin and ***resveratrol were found to be aromatase inhibitors*** in this co-culture system, albeit at different concentrations. The co-culture model ***did not provide any indications that melatonin is also a selective estrogen receptor modulator (SEEM)***. In the T47D-BAF co-culture, ***a melatonin concentration of 20 nM*** and ***resveratrol concentration of 20 µM had an aromatase inhibitory effect as potent as 20 nM letrozole***, which is a clinically used anti-aromatase drug in breast cancer treatment. ***The SEEM mechanism of action, especially of melatonin, clearly offers potential advantages for breast cancer treatment*** (Chottanapund et al., 2014).

Current evidence indicates that ***alterations of the intracellular redox state play a key role in the effects of high concentrations of phytomelatonin in cancer cells***, reducing conditions associated with a ***decrease in cell proliferation*** and ***oxidative conditions with apoptosis***. The last data may be in conflict with the fact that high concentrations of phytomelatonin show clear antioxidant properties. Furthermore, unlike other antioxidants, such as vitamins C or E, phytomelatonin oxidation results in metabolites that still possess antioxidant properties. Thus, the key question remains: why are reactive oxygen species (ROS) elevated in some cancer cells upon their treatment with high concentrations of phytomelatonin? These researchers believe that a primary pro-oxidant effect of this indole could be ruled out, bearing in mind the data so far demonstrated and the fact that an ***increase in ROS is not a general fact***, ***but an exception*** observed only with cancer studies. A fact to be considered is that the metabolism of cancer versus normal cells shows numerous differences. Metabolism can also differ between different cancer cell types. However, for now those are only speculative, and the actual explanation remains to be fully elucidated. Future research study addressing this question is essential to understand the exact mechanisms by which phytomelatonin achieves its antitumoral and apoptotic activities will be a major challenge in the field of phytomelatonin research. The fruits from such labor could contribute toward improved oncological therapies with some particular cancer types (Rodriguez et al., 2013).

Phytomelatonin can act as an anticarcinogenic and ***antitumor agent***. This effect has been studied in multiple cancers including breast, lung, liver, renal, pancreatic, colorectal, testicular, endometrial, cervical-vaginal, skin, and brain, as well as lymphoma. The action of phytomelatonin on cancer cells has been related with its ability to reduce DNA damage, upregulate antioxidative enzymes, change the expression of growth- and differentiation-related genes, and reduce some mitogenic signals, apoptosis, and the antimetastatic capacity of tumor cells through the control of certain oncogenesis-related genes, among others. A number of cancers have been shown associated with low melatonin levels or with deficiencies of melatonin-receptors in damaged tissues. Some therapies use phytomelatonin to arrest tumor proliferation and with better results than from synthetic or animal source (Arnao & Hernández-Ruiz, 2018).

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). Phytomelatonin is also present in significant amounts in edible and medicinal plants and is supplied in nutritional supplements. Here was confirmed the presence of significant

quantities of phytomelatonin in 20 varieties of edible plants. In pinealectomized tumor-free rats, 3 weeks of ingestion of either 5 or 50 microg/day of phytomelatonin contained in a semi-purified diet resulted in a dose-dependent elevation in steady-state plasma melatonin levels within the nocturnal physiological range. In pineal-intact tumor-bearing rats, the daily intake of ***5 microg/day of phytomelatonin for 3 weeks resulted in an enhanced amplitude*** *and* ***duration of the nocturnal melatonin levels within physiological circulating limits***. The nocturnal melatonin amplitude in rats ingesting 500 ng of phytomelatonin/day remained within the physiological range. A dose-related increase in tumor concentrations of melatonin occurred in animals ingesting phytomelatonin from the diet. Perfusion of tumors *in situ* with physiological, nocturnal blood levels of melatonin resulted in a mean ***31% uptake*** and retention of the phytomelatonin. Chronic ingestion of 50 ng, 500 ng, or 5 microg of phytomelatonin/day supplied in a semi-purified 5% corn oil diet led to ***a significant dose-dependent reduction in the rates of tumor total fatty acid uptake***, ***LA uptake***, ***13-HODE production****,* and ***tumor growth***. The co-ingestion of melatonin receptor antagonist S20928 completely blocked the effects and prevented the intra-tumoral accumulation of phytomelatonin. Melatonin receptor-mediated suppression of tumor growth, LA uptake and metabolism, and stimulation of tumor melatonin uptake and retention in response to the dietary intake of phytomelatonin from edible plants, could play an important role in cancer growth prevention against liver cancer (Blask et al., 2004).

Melatonin has anticarcinogenic properties in experimental models. Researchers undertook a case-cohort study of 928 Icelandic men without prostate cancer (PCa) nested within the Age, Gene/Environment Susceptibility (AGES)-Reykjavik cohort to investigate the prospective association between first morning-void urinary 6-sulfatoxymelatonin (aMT6s) levels and the subsequent risk for PCa, under the hypothesis that men with lower aMT6s levels have an increased risk for advanced PCa. In this study, they used weighted Cox proportional hazards models to assess the association between first morning-void aMT6s levels and PCa risk, adjusting for potential confounders. A total of 111 men were diagnosed with incident PCa, including 24 with advanced cancer. Men who reported sleep problems at baseline had lower morning aMT6s levels compared with those who reported no sleep problems. ***Men with morning aMT6s levels below the median had a fourfold statistically significant increased risk for advanced disease compared with men with levels above the median*** (hazard ratio: 4.04; 95% confidence interval, 1.26-12.98). These results require replication in larger prospective studies with longer follow-up. This report evaluated ***the prospective association between urinary aMT6s levels*** and ***risk of PCa in an Icelandic population*** and ***concluded that lower levels of aMT6s were associated with an increased risk for advanced PCa*** (Sigurdardottir et al., 2015).

In another study, melatonin and clonazepam were each reported ***to reduce sleep behavior disorder (RBD) behaviors*** and ***injuries*** and ***appeared comparably effective in the researchers' naturalistic practice experience***. ***Melatonin-treated patients reported less frequent adverse effects than those treated with clonazepam***. More effective treatments that would eliminate injury potential and evidence-based treatment outcomes from prospective clinical trials for RBD are needed (McCarter et al., 2013).

Klonopin is the brand name for clonazepam, a benzodiazepine medication prescribed to stop panic attacks, manage anxiety disorders, treat insomnia, and reduce the risk of

seizures for people with seizure disorders like epilepsy. Generally, benzodiazepines like Klonopin work with the gamma-aminobutyric acid (GABA) receptors in the brain to reduce the frequency of electrical activity. Depending on the dose, this can lead to a feeling of relaxation, sleepiness, or intoxication. Many of the more serious effects associated with Klonopin involve changes to brain function. These may include slowed thinking, great difficulty concentrating, reduced motor coordination or fine motor skills, dizziness, sleepiness, and memory damage, as well as serious psychological side effects, including depression, suicidal thoughts, worsened anxiety or depression, impulse control problems, and similar problems. None of these side effects have been reported with the use of phytomelatonin (McCarter et al., 2013).

Klonopin medication is part of a larger group of substances called the benzodiazepines. This group includes substances like: Alprazolam (Xanax), Lorazepam (Ativan), Diazepam (Valium), and Temazepam (Restoril). Long-term use of benzodiazepines like Klonopin has been linked to an increased likelihood of developing Alzheimer's disease later in life, by as much as 51%. Benzodiazepine use is associated with an increased risk of Alzheimer's disease. The stronger association observed for long-term exposures reinforces the suspicion of a possible direct association, even if benzodiazepine use might also be an early marker of a condition associated with an increased risk of dementia. Unwarranted long-term use of these drugs ***should be considered a public health concern***. A case-control study based on 8,980 elderly people living in the community of Quebec showed that the risk of Alzheimer's disease was increased by ***43-51%*** among those who had used benzodiazepines in the past. ***Risk increased with density of exposure*** and ***when long-acting benzodiazepines were used***. Further adjustment on symptoms thought to be potential prodromes for dementia—such as depression, anxiety, or sleep disorders—did not meaningfully alter the results (Billioti de Gage et al., 2014).

A study concluded that ***melatonin production clearly declined with age*** but was not influenced by other demographic variables or by season of the year (Sack et al., 1986).

Dementia with Lewy bodies is an under-recognized disease; it is responsible for up to 20% of all dementia cases. Accurate diagnosis is essential because the management of dementia with Lewy bodies is more complex than many neurodegenerative diseases. This is because alpha-synuclein, the pathological protein responsible for dementia with Lewy bodies (and Parkinson's disease), produces symptoms in multiple domains. By dividing the symptoms into cognitive, neuropsychiatric, movement, autonomic, and sleep categories, a comprehensive treatment strategy can be achieved. Management decisions are complex, since the treatment of one set of symptoms can cause complications in other symptom domains. Nevertheless, a comprehensive treatment program can greatly improve the patient's quality of life, but does not alter the progression of disease. Cholinesterase inhibitors are effective for cognitive and neuropsychiatric symptoms; rivastigmine has the widest evidence base. Special care needs to be taken to avoid potentially fatal idiopathic reactions to neuroleptic medications; these should be used for short periods only when absolutely necessary and when alternative treatments have failed. Pimavanserin, a selective serotonin 5-HT2A inverse agonist, holds promise as an alternative therapy for synuclein-associated psychosis. Levodopa/carbidopa treatment of Parkinson's is often limited by dopa-induced exacerbations of neuropsychiatric and cognitive symptoms. Autonomic symptoms are under-recognized complications of

synucleinopathy. Constipation, urinary symptoms and postural hypotension respond to standard medications. Rapid eye movement sleep behavior disorder is highly specific (98%) to the synucleinopathies. ***Nonpharmacological treatments***, ***melatonin***, and ***clonazepam are all effective*** (Boot, 2015).

Please note: There are many causes of insomnia – melatonin deficiency is only one – and this needs to be especially emphasized when someone has a paradoxical effect to any types of synthetic melatonin or phytomelatonin supplementation, which clearly indicate that melatonin levels are sufficient or when a dose is too high, with the long-term use of phytomelatonin, and when the pineal gland has reached optimal levels of melatonin. A good indicator of this is repeated nightmares, which should indicate that it's time to reduce the dose. Note: never abruptly discontinue, but rather gradually reduce until nightmares subside. When this reoccurs with a reduced dose, once more reduce the dose until the insomnia is corrected. However, this will often also require the use of Passion Flower – Passiflora Incarnata (bud of flowers) to decalcify the pineal gland at a dose of 15 gtts, tid, QD given anywhere from six to 18 months to return the pineal gland to a normal size.

In post-menopausal or male andropause, often there is a missing link to insomnia being caused by one or more reasons, especially when having low progesterone level. For this, you need to give Chaste Tree – Vitex Agnus Castus (young shoots) at a dose of 15-25 gtts, tid, PRN, QD. When caused by low serotonin level the best MAO A and B inhibitor is Linden Tree – Tilia Tomentosa (bud of leaves) the *polycrest* at a dose of 15 to whatever dose needed (ad libitum, PRN), tid, qid or given 1½ hour before bedtime take 50-100-150 gtts. Difficulty falling asleep requires Passion Flower – Passiflora Incarnata (bud of flowers) taken during the day, 15 drops 3 x a day and/or Valerian – Valeriana Officinalis (embryonic roots) 15-25 gtts, tid, QD, PRN – or a much higher dose, like 30-100 gtts 1½ hour before bedtime. In some cases, you may need both. For interrupted sleep, you need California Poppy – Eschscholzia Californica (bud of leaves) 30 gtts every time you wake up, and in this way with time break the pattern of interrupted sleep. In some stubborn and tenacious cases, you may need all of these plants in addition to others. The combinatorial use of these plants needs to be given on an individual basis, as no one fits all.

Most studies have shown that short-term melatonin-phytomelatonin use is safe for children with little to no side effects. Phytomelatonin-containing medicinal plants were shown superior for children with sleep disorders due to other phytochemicals present within a whole plant composition.

However, you can increase your melatonin levels without any supplements. A few hours before bedtime, simply dim all the lights in your home and avoid watching TV and using your computer or cellphone. Too much artificial light can reduce the production of melatonin in the brain, making it more difficult for you to fall asleep.

Children with neurodevelopmental disorders have a higher prevalence of sleep disturbances. Currently there is variation in the use of melatonin; hence, an up-to-date systematic review is indicated to summarize the current available evidence. They identified 3262 citations and included 13 studies in this meta-analysis. Main outcomes included total sleep time, sleep onset latency, frequency of nocturnal awakenings, and adverse events. Thirteen randomized controlled trials (n=682) met the inclusion criteria.

A meta-analysis of nine studies (n=541) ***showed that melatonin significantly improved total sleep time compared with placebo*** (mean difference (MD)=48.26 min, 95% CI 36.78 to 59.73, I^2=31%). In 11 studies (n=581), ***sleep onset latency improved significantly with melatonin use*** (MD=-28.97, 95% CI -39.78 to -18.17). No difference was noted in the frequency of nocturnal awakenings (MD=-0.49, 95% CI -1.71 to 0.73). No medication-related serious adverse event was reported. This review of all the data research concluded that melatonin ***appeared safe*** and ***effective in improving sleep in the studied children***. However, the overall quality of evidence is limited due to heterogeneity and inconsistency. Further research is still required to fully elucidate long-term benefits (Abdelgadir et al., 2018).

Sleep deprivation among adolescents is also epidemic. We argue that this sleep deprivation is due in part to pubertal changes in the homeostatic and circadian regulation of sleep. ***These changes promote a delayed sleep phase that is exacerbated by evening light exposure*** and ***incompatible with aspects of modern society***, ***notably early school start times***. This review of human and animal literature demonstrated that delayed sleep phase during puberty is likely a common phenomenon in mammals, not specific to human adolescents, and they provided insight into the mechanisms underlying this phenomenon (Hagenauer et al., 2009).

Another recent meta-analysis on melatonin has raised doubts as to whether melatonin is effective in treating sleep problems in people without intellectual disabilities. ***This is in contrast to results of several trials on melatonin in treating sleep problems in individuals with intellectual disabilities***. To investigate the efficacy of melatonin in treating sleep problems in individuals with intellectual disabilities, they performed a meta-analysis of placebo-controlled randomized trials of melatonin in individuals with intellectual disabilities and sleep problems. Data were selected from articles published on PubMed, Medline, and Embase between January 1990 and July 2008. They examined the influence of melatonin on sleep latency, total sleep time, and number of wakes per night. Quality of trials was assessed using the Downs and Black checklist. Nine studies (including a total of 183 individuals with intellectual disabilities) ***showed that melatonin treatment decreased sleep latency by a mean of 34 minutes (p<0.001)***, ***increased total sleep time by a mean of 50 minutes (p<0.001)***, and ***significantly decreased the number of wakes per night (p<0.05)***. ***Melatonin does decreases sleep latency*** and ***number of wakes per night,*** and ***increases total sleep time in individuals with intellectual disabilities*** (Braam et al., 2009).

Melatonin in autism spectrum disorders (ASD): a systematic review and meta-analysis. The aim of another review was to investigate melatonin-related findings in ***ASD***, ***including autistic disorder***, ***Asperger syndrome***, ***Rett syndrome***, and ***pervasive developmental disorders*** not otherwise specified. The interpretation from these nine studies concluded that ***melatonin administration in ASD is indeed associated with improved sleep parameters***, ***better daytime behavior***, with ***minimal side effects***. Additional studies of melatonin would be helpful to confirm and expand on these findings (Rossignol & Frye, 2011).

Yet another study evaluated the efficacy and safety of ***melatonin for the treatment of insomnia in pediatric patients with attention-deficit/hyperactivity disorder (ADHD)***. Pediatric insomnia is prevalent in children with ADHD and impacts academic

performance, social functioning, overall health, and family life. First-line therapy includes ruling out differential diagnoses, ***optimizing ADHD stimulant treatment***, and ***initiating good sleep hygiene*** *and* ***behavioral therapy***. ***Adjuvant pharmacotherapy is then an option*** and ***melatonin often prescribed***. Melatonin regulates circadian rhythm sleep disorders such as ***sleep-onset insomnia (SOI)*** in children with ADHD. Four studies in children with ADHD and insomnia showed improvement in sleep onset and sleep latency. Studies included children 6-14 years old and melatonin doses ranged from 3 to 6 mg administered within a few hours of a scheduled bedtime. In all studies, adverse events were transient and mild. The available melatonin studies are limited by small size and short duration; variable SOI criteria, ADHD criteria, and treatment assessments; and lack of generalizability. The conclusion from available data ***does suggest that melatonin is a well-tolerated*** and ***efficacious treatment option for pediatric patients with chronic SOI*** and ***ADHD***. Regulated melatonin products and larger, well-designed trials to establish optimal dosing regimens and long-term safety are needed (Bendz & Scates, 2010).

Some supplemental melatonin users report an increase in vivid dreaming. Extremely high doses of melatonin increased REM sleep time and dream activity in people both with and without narcolepsy (Lewis, 1999).

Melatonin and the pineal gland have primarily been considered in terms of their effects on the endocrine and reproductive systems. During the last decade, a substantial body of research has defined melatonin as a remarkable molecule with pleiotropic (producing more than one effects) on the immune system. Moreover, its synthesis cannot be considered as exclusively endocrine; key immunocompetent cells have the functional enzymatic machinery for melatonin synthesis, ***paving the way for complex intracrine***, ***autocrine,*** and ***paracrine regulatory loops***. The ***immunomodulatory role of melatonin***, with regard to infection, inflammation, and autoimmune response, is outlined here, and the evidence discussed in this review ***strengthens the notion that the nature of an immune response may be modified***, and ***therefore therapeutically manipulated, by circadian effector signals*** (Carrillo-Vico et al., 2006).

We know from many studies that sleep-deprived individuals end up with lowered immunity and that sleep is so critical for a good working immune system competency. Furthermore, is the role of the pineal gland and its role on the immune system. The pineal gland constitutes a major neuroendocrine organ in the brain. It transduces exogenous signals such as circadian and seasonal variations of light and temperature into proper hormonal changes, which adjust and adapt internal endocrine functions. These pineal activities seem to be exerted *via* circadian synthesis and release of the indoleamine melatonin, a neurohormone secreted by the pineal itself. Alteration of circadian rhythms have been associated with affective disorders, psychosomatic diseases, cancer, and many other pathologies. These researchers have reported that functional and pharmacologic inhibition of melatonin synthesis results in depressed immune functions *in vivo* and that exogenous, evening administration of melatonin enhances antibody formation *via* an antigen-activated process and also antagonizes the immunosuppressive effects of corticosterone. Here they communicate findings demonstrating that (a) three different inbred strains of mice possess a clear-cut cycle of melatonin levels in serum, (b) melatonin administered in the evening enhances primary antibody response (IgM and IgG

immunoglobulins) *in vivo* according to a dose-response behavior, and (c) the opioid receptors blocker naltrexone antagonizes the immunostimulatory effect of melatonin. These findings point to a fundamental ***immunoregulatory role of circadian melatonin*** and to ***an activity of the neurohormone via opioid peptides*** (Maestroni et al., 1987).

Although radiotherapy is a common and effective tool for cancer treatment, the radio-sensitivity of normal tissues adjacent to the tumor that are unavoidably exposed to radiation limits therapeutic gain. For the sake of improvement in radiation therapy, radiobiology – the study of the action of ionizing radiation on living things – plays a crucial role through explaining observed phenomena and suggesting improvements to existing therapies. ***Due to the damaging effects of ionizing radiation***, radiobiologists have long been interested in identifying novel, nontoxic, effective, and convenient compounds to protect humans against radiation-induced normal tissue injuries. ***In hundreds of investigations, melatonin (N-acetyl-5-methoxytryptamine)***, the chief ***secretory product of the pineal gland in the brain***, ***has been documented to ameliorate the oxidative injuries due to ionizing radiation***. This article reviews different features that make melatonin ***a potentially useful radioprotector***. Moreover, based on radiobiological models, it is hypothesized that ***melatonin may postpone the saturation of repair enzymes, which leads to repairing more induced damage by repair system****, and* ***more importantly allows the use of higher doses of radiation during radiotherapy to get a better therapeutic ratio***. The implications of the accumulated observations suggest that by virtue of melatonin's radioprotective and anticancer effects, it is time to use it as a radioprotector for both radiation workers and patients suffering from cancer – either alone for cancer inhibition or in combination with traditional radiotherapy for getting a favorable efficacy/toxicity ratio during the treatment. Although compelling evidence suggests that melatonin may be effective for a variety of disorders, the optimum dose of melatonin for human radioprotection is yet to be determined (Shirazi et al., 2007).

A review of the literature included six publications with 125 participants (106 aged under 18 years). Two different comparisons were available: melatonin versus placebo and melatonin 5 mg versus melatonin 10 mg. Despite their primary intention, due to insufficient information on outcomes, they were unable to perform any meta-analyses, but summarized data narratively. Four studies were randomized, double-blind, cross-over, placebo-controlled trials and two were randomized, double-blind, parallel, placebo-controlled trials. Only two studies provided the exact number of seizures during the trial compared to the baseline: none of the participants with seizures during the trial had a change in seizure frequency compared with the baseline. Two studies systematically evaluated adverse effects (worsening of headache was reported in a child with migraine under melatonin treatment). Only one study systematically evaluated quality of life, showing no statistically significant improvement in quality of life in the add-on melatonin group. Included studies were of poor methodological quality and did not systematically evaluate seizure frequency or adverse events, so that it was impossible to summarize data in a meta-analysis. It is not possible to draw any conclusion about the role of melatonin in reducing seizure frequency or improving quality of life in people with epilepsy (Brigo et al., 2016).

Gastro-Esophageal Reflux Disease (GERD) is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.

Many drugs are used for the treatment of GERD, such as omeprazole (a proton pump inhibitor), a widely used antiulcer drug demonstrated to protect against esophageal mucosal injury. ***Melatonin has been found to protect the gastrointestinal mucosa from oxidative damage caused by reactive oxygen species (ROS)*** in different experimental ulcer models. The aim of this study was to evaluate the role of exogenous melatonin in the treatment of GERD in humans, either alone or in combination with omeprazole therapy. 36 persons were divided into 4 groups (control subjects, patients with reflux disease treated with melatonin alone, omeprazole alone, and a combination of melatonin and omeprazole for 4 and 8 weeks) Each group consisted of 9 persons. Persons were subjected to thorough history taking, clinical examination, and investigations including laboratory, endoscopic, record of esophageal motility, pH-metry, basal acid output, and serum gastrin. ***The results showed that melatonin does play a role in the improvement of GERD when used alone*** or in combination with omeprazole. Meanwhile, omeprazole alone is better used in the treatment of GERD than melatonin alone. The present study showed that oral melatonin is a promising therapeutic agent for the treatment of GERD. It is an ***effective line of treatment in relieving epigastric pain*** and ***heartburn*** (Kandil et al., 2010).

Melatonin—a tiny tryptophan derivative in the bovine pineal extract. Since then, this wonder molecule is known to regulate a wide variety of physiological and psychological activities of lower and higher vertebrates, including human beings. ***The exact mechanisms of melatonin actions are poorly understood*** and ***explained to date***, but the coexistence of endocrine, paracrine, autocrine, and intracrine actions and feedback effects are suggested mostly to be mediated by the specific receptors found in the respective target organs. ***Melatonin exhibits a remarkable contextual diversity of functions as circadian pacemakers***, ***hypothalamic/pituitary (HPG) axis to vasomotor effects***, ***immunomodulatory***, ***antioxidative actions***, ***anti-apoptotic effects (direct*** *and* ***indirect)***, etc. With such efficacy and safety, melatonin may therefore eventually drive its use ***with other plant extracts containing phytomelatonin in universally effective clinical applications*** and ***an adjuvant therapy***, ***especially for Polycystic Ovarian Syndrome (PCOS)***, for treatment in near future and can be proved as a best medicinal tool. In mammalian species, ***melatonin affects reproductive function partially by activating receptor sites within the HPG axis***. ***The effect of melatonin on ovarian function varies with tissue structure***, ***cell type***, and whether the species is a seasonal or non-seasonal breeder. The present review aimed to summarize in brief the role of ***melatonin in regulation of reproduction during the PCOS condition***. Knowingly, ***melatonin is per se neither anti-gonadotropic nor pro-gonadotropic but changing the duration of nocturnal melatonin provides message signal to the HPG axis*** about the information of calendar year. The reproductive axis ***uses the melatonin rhythm to adjust ovarian physiology accordingly***. ***PCOS is the common endocrine disorder of unknown etiology***. ***During PCOS***, ***hypothalamic gonadotropin-releasing hormone (GnRH) declines the optimum concentration*** and ***melatonin***, ***having an inverse relation with the hypothalamic GnRH*** (a decapeptide), ***released in a pulsatile fashion from neuro secretory cell of hypothalamus to regulate the production*** and ***release of the follicle-stimulating hormone (FSH)*** and ***luteinizing hormone (LH) from anterior pituitary***. Thus, this review summarizes the edible plants listed for the presence of phytomelatonin. Such plant extracts containing

phytomelatonin may be used during PCOS pathogenesis under the new pharmacological strategies to explore a novel therapeutic molecule in the treatment of PCOS (Basheer Muddasir & Seema, 2016).

The novel use of phytomelatonin on the clinical management of menopausal symptoms and ***menopausal osteoporosis*** has been investigated. A study with phytomelatonin proposed ***mode of actions to normalize estrogen*** and ***progesterone levels****,* improving symptoms associated with perimenopause. Melatonin, *via* its ***actions on the ovary***, ***is proposed to normalize estrogen*** and ***progesterone levels***. Melatonin, by ***enhancing inhibin B release to lower FSH levels*** as well as through its inhibitory ***actions on aromatases*** and ***17β-hydroxysteroid dehydrogenase*** type 1 is proposed to lower estrogen levels. ***Melatonin is proposed to decrease FSH levels via increases in inhibin B levels*** and ***inhibin B is known to suppress the gonadotropic axis***. ***Melatonin is also proposed to raise progesterone levels***. Melatonin-mediated increases in progesterone and decreases in FSH and estrogen are proposed to improve health in perimenopausal symptoms (i.e., menorrhagia, uterine fibroids, bone loss), attributed to disrupted hormonal profiles. This study hypothesized that melatonin may be resynchronizing these disrupted hormonal rhythms through its actions on the ovary decreasing FSH-mediated bone resorption, while increasing progesterone-mediated bone formation. Much of the research studying the efficacy of medicinal plants to prevent or treat disease ***is focused only on a reductionistic approach****, trying to find "the one" compound within a plant responsible* for the health-promoting effect, when in fact, ***plants produce multiple phytochemicals and research in this area of natural products should concentrate more on the interactions*** between the many phytochemicals found within a plant rather than on one or two, and determine how these interactions result in positive health outcomes. In addition to the animal testing, ***studies performed in humans have clearly shown that consumption of phytomelatonin-rich medicinal plant or food source results in significant levels of melatonin in the blood*** *and* ***correlate with a significantly higher antioxidative capacity***. This study showed that 3 mg nocturnal consumption of melatonin produced significant and positive effects on menopausal symptoms in women and prevented the onset of osteoporosis by increasing progesterone, which increased bone formation (Lassila et al., 2014).

According to recent research, ***phytomelatonin*** especially has also a great ***antiaging effect***. Like the whole organism, skin follows the process of aging during lifetime. Additional to ***internal factors***, ***several environmental factors***, such as ***solar radiation***, considerably contribute to skin aging. While fundamental ***mechanisms regarding skin aging*** are known, new aspects of ***antiaging agents such as phytomelatonin*** are introduced. ***It has been experimentally implicated in skin functions****, such as hair cycling* and ***fur pigmentation***, and ***melatonin receptors are expressed in many skin cell types including normal*** and ***malignant keratinocytes***, ***melanocytes****,* and ***fibroblasts***. It possesses ***a wide range of endocrine properties as well as extremely potent antioxidative activity***. ***Regarding UV-induced solar damage***, ***melatonin distinctly counteracts massive generation of reactive oxygen species (ROS)***, ***mitochondrial*** and ***DNA damage***. Thus, there is considerable evidence for melatonin to be an effective skin antiaging compound. Also, ***unlike classic antioxidants***, ***melatonin does not induce prooxidant reactions***. For years and in many investigations, great and convincing evidence revealed that melatonin and its potent antioxidative properties shows

a tremendously broad spectrum of action such as ***bioregulatory as well as pluripotent*** and ***essential protective effects in many cells***, ***tissues,*** and ***compartments of unicells***, ***animals,*** and the ***human body***. The predominant feature of melatonin therein is that of a ***potent cyto-*** and ***tissue-protective substance on multiple molecular*** and ***cellular damage levels*** and ***mechanisms***, both in physiological and pharmacological concentrations. The fact that the ***essential enzymes for melatonin synthesis are expressed in skin cells*** and ***cutaneous tissue at a great variety***, and that skin ***cells are able to produce autonomously melatonin*** and to develop metabolism with the generation of metabolites with strong antioxidative properties, ***renders the skin a major extra-pineal site of melatonin production*** and activity. Moreover, solar ***UV irradiation is one of the main environmental skin stressors*** and it ***is significantly counteracted or modulated by melatonin in the context of a complex intracutaneous melatoninergic antioxidative system of the skin***. Regarding clinical application, exogenous melatonin should rather be used topically than orally, since orally administered melatonin appears in rather low levels in the blood due to prominent first-pass degradation in the liver, thus limiting skin access. Topical application might be meaningful, since melatonin can penetrate into the stratum corneum and build a depot due to its distinct lipophilic chemical structure. Therefore, endogenous intracutaneous melatonin production, together with topically applied exogenous melatonin or metabolites, can be expected to ***represent one of the most potent antioxidative defense systems against UV-induced skin aging*** (Kleszczynski, & Fischer, 2012).

Melatonin has been shown to have oncostatic effects on malignant melanoma in vitro and ***in vivo***. Here was studied the growth suppressive effects of melatonin over a wide range of concentrations in four melanoma cell lines (SBCE2, WM-98, WM-164, and SKMEL-188) representative for different growth stages and phenotype. Melanoma cells were incubated with melatonin 10(-12)-10(-3) M, and proliferation and clonogenicity was assessed at 12 h and 14 days, respectively. They also determined the expression of cytosolic quinone oxidoreductases NQO1, NQO2 (known as MT3 receptor) and nuclear receptor RORα by RT-PCR. Melatonin at pharmacological concentrations (10(-3)-10(-7) M) ***suppressed proliferation in all melanoma cell lines***. In SKMEL-188 cells cultured in serum-free media, melatonin at low concentrations (10(-12)-10(-10) M) also *slightly attenuated the proliferation*. The effects of pharmacological doses of melatonin were confirmed in the clonogenic assay. Expression of NQO1 was detected in all cell lines, whereas NQO2 and nuclear receptor RORα including its isoform RORα4 were present only in SBCE2, WM-164, and WM-98. Thus, ***melatonin differentially suppressed proliferation in melanoma cell lines of different behavior***. ***The intensity of the oncostatic response to melatonin*** could be related to the cell-line specific pattern of melatonin cellular receptors and cytosolic binding protein expression (Fischer et al., 2006).

Melatonin, a pineal indolamine, participates in different body functions and is shown to possess diverse biological activities such as anti-tumor action. Angiogenesis inhibition is one of the mechanisms by which ***melatonin exerts its oncostatic effects***. Increased angiogenesis is a major feature of tumor progression, and ***thus angiogenesis inhibition is a critical step in cancer therapy***. Melatonin employs a variety of mechanisms to target nutrients and oxygen supply to cancer cells. At the transcriptional level, ***hypoxia induced factor-1α (HIF-1α)*** and the genes under its control, such as ***vascular endothelial***

growth factor (VEGF), are the main targets of melatonin for inhibition of angiogenesis. Melatonin prevents translocation of HIF-1α into the nucleus, thereby hindering VEGF expression, and also prevents the formation of HIF-1α, phospho-STAT3, and CBP/p300 complex which is involved in the expression of angiogenesis-related genes. Angiostatic properties of melatonin could be also due to its ability to ***inhibit VEGFR2's activation*** and ***expression***. Other angiostatic mechanisms of melatonin include the inhibition of endothelial cell migration, invasion, and tube formation. This study reviewed the molecular ***antiangiogenesis pathways mediated by melatonin*** and ***the responsible mechanisms in various types of cancers*** both *in vitro* and *in vivo* (Goradel et al., 2017).

Data regarding the protective effects of food rich in melatonin/phytomelatonin in liver pathological conditions currently are not available. Nevertheless, the collected studies could suggest that the health-promoting effects ascribed to a dietary style with ***increasing of blood melatonin levels may be considered a promising preventive approach for a variety of liver diseases***. In particular, ***melatonin/phytomelatonin leads to the preservation of cellular homeostasis via downregulation of oxidative stress*** also ***at mitochondrial level***. In these ***latter organelles, melatonin/phytomelatonin enters through specific oligopeptide transporters (PETP1/2)*** and ***performs its multiple functions***. These actions, especially ***its antioxidant function, preserve mitochondrial function*** and benefit diseases in which mitochondrial malfunction is a feature, including liver diseases. ***An important take-home message from this review is that melatonin should not be thought of as a "regular antioxidant" in liver disease***. ***The mere fact that it is both consumed in the diet*** and ***produced makes melatonin unique***. Additionally, the fact that ***melatonin is associated with mitochondria should make it of significant interest in any study in which the endpoints include deferring the onset of diseases*** and ***improving the quality of life***. However, it is important to report that the health benefits attributed to plant foods and Mediterranean or other diets ***could not depend on a single compound present in them*** (phenolic, carotenoid, etc.), ***but rather a combination of other substances enhance the actions, inducing synergic effects***. Moreover, another limitation in the use of this indoleamine for targeting oxidative damage in liver is the fact that much of the results are derived from studies on animal models and there are very few clinical trial studies. So, more research is needed to strengthen the potential beneficial effects of dietary melatonin/phytomelatonin in liver pathological conditions (Bonomini et al., 2018).

A study quantified melatonin in 30 commercial supplements comprising different brands and forms and screened supplements for the presence of serotonin. Melatonin content was found to range from −83% to +478% of the labelled content. Additionally, lot-to-lot variable within a particular product varied by as much as 465%. This variability did not appear to be correlated with manufacturer or product type. Furthermore, serotonin (5-hydroxytryptamine), a related indoleamine and controlled substance used in the treatment of several neurological disorders, was identified in eight of the supplements at levels of 1 to 75 μg. This study concluded that melatonin content did not meet label within a 10% margin of the label claim in more than 71% of supplements, and an additional 26% were found to contain serotonin. It is important that clinicians and patients have confidence in the quality of supplements used in the treatment of sleep disorders. To address this, manufacturers require increased controls to ensure melatonin supplements both meet

their label claim and also are free from contaminants, such as serotonin (Erland & Saxena, 2017).

Contraindications: Do not use melatonin if you are pregnant, lactating, have epilepsy or migraines, are taking warfarin, or if you have a personal or family history of psychiatric disorders, whereas ***phytomelatonin*** is usually fine when part of a whole plant extract. Again, and again, the problem always seems to be caused by synthetic isolates.

DO NOT combine melatonin or phytomelatonin with other synthetic sedatives. Avoid alcohol and sedating medications when taking melatonin or phytomelatonin.

Biological activities include: adaptogen, anaphrodisiac, antiaggregant, antiaging of the skin, antiAlzheimeran, antiangiogenesis, anticancer (breast, colon, liver, melanoma, prostate), anticarcinogenic, anticholelithiasis, anticlimatric (hot flashes), anticonvulsant, antidementia, antidepressant, antidyspepsia, antiGERD, antigonadotrophic, anti-hypoxic, antiinflammatory, antiinsomniac, anti-jet lag, antimetabolic syndrome, antineurodegenerative, antiobesity, antiosteoporotic, antioxidative, antiPCOS, antiproliferative, antiradicular, antirheumatic, antisenescence, antithyreotropic, antitinnitus, antitumor, aphrodisiac, apoptotic, aromatase inhibitor, chemoprevention, contraceptive, counteracts massive generation of ROS, COX-2 inhibitor, cytokines modulator, cytoprotective, DNA repair, GABA-nergic, gastroprotective, GnRH modulator, gonadotrophic, hepatoprotective, HIF-1α inhibitor, hypnotic, hypocholesterolemic, hypothermic, immunomodulator, immunostimulant, improves concentration and cognitive function, increases ATP, increases REM sleep, increases SRT1, increases CAT, GSH, and SOD detoxifying liver enzymes, inducer of autophagy, LH and FSH modulator, PGE_2 inhibitor, potent antioxidant, preserves mitochondrial function, progesterone agonist, progesteronigenic, protects mitochondria, radical scavenger, radioprotective, repairs mPTP, retains CNPase enzyme, ROS inhibitor, serotoninergic, telomeres lengthening and maintenance, thyrotropic, toxic metals chelator, and UV solar damage inhibitor, VEGF and VEGFR2 inhibitor (Duke, 1992; Richard, 2019).

THE PINEAL GLAND is a tiny endocrine gland located in the epithalamus, near the center of the brain between the two hemispheres, tucked in a groove where the two halves of the thalamus join. The shape of the pineal gland resembles a pine cone, from which its name was derived (Macchi & Bruce, 2004).

Pineal Gland Functions

- The pineal gland produces melatonin, a serotonin-derived hormone that modulates sleep patterns in both circadian and seasonal cycles. Melatonin is referred to as a chronobiotic, which is an agent that can cause phase adjustment of the body clock (Arendt & Skene, 2005).
- The pineal gland influences the pituitary gland's secretion of the sex hormones, follicle-stimulating hormone (FSH), and luteinizing hormone (LH).
- Secretion of the hormone melatonin.
- Governs and regulates pigmentation.
- Regulation of endocrine functions.
- Conversion of nervous system signals to endocrine signals.

- Causes sleepiness.
- Influences sexual development.
- Involved in intuition. Interestingly, the pineal gland has been linked to the production of the psychoactive compound called *N*,*N*-dimethyltryptamine (DMT), (Strassman, 1991; Strassman & Qualls, 1994). However, it remains controversial that the pineal gland produces DMT although it does occur in the brain.
- Influences the immune system function.
- Potent antioxidant activity.
- Melatonin influences the development of reproductive system structures, as well. It inhibits the release of certain reproductive hormones from the pituitary gland that affect male and female reproductive organs. These pituitary hormones, known as gonadotropins, stimulate gonads to release sex hormones. Melatonin therefore regulates sexual development.

Pineal Gland Dysfunction

Should the pineal gland begin to function abnormally, a number of problems could ensue. A person could experience insomnia, anxiety, low thyroid hormone production (hypothyroidism), menopause symptoms, or intestinal hyperactivity. If the pineal gland produces too much melatonin, a person could experience low blood pressure, abnormal function of the adrenal and thyroid glands, or Seasonal Affective Disorder (SAD).

Pineal Gland Calcifies with Aging

The pineal gland gets hardened, then calcified, and eventually shuts down. It is also suppressed by electromagnetic fields (EMF) released by mobile phones and other wireless devices. The pineal gland is especially sensitive to fluoride in the water. Fluoride and other chemical substances like chlorine are bad for the pineal as they deposit on tissues that are rich in calcium, such as the pineal. The gland calcifies when it encounters fluoride – these calcifications are known as corpora arenacea, or brain sand, and are made up of calcium phosphate, calcium carbonate, magnesium phosphate, and ammonium phosphate.

With aging and old age, the pineal gland contains about the same amount of fluoride as teeth. By old age, the pineal gland has readily accumulated fluoride and its F/Ca ratio is higher than bone (Luke, 2001).

Chemicals that are harmful to the pineal gland can come from everyday activities – for example, fluoride is found in most toothpastes and tap water. Likewise, food laden with pesticides, preservatives, and chemicals causes the pineal gland to become sluggish and lose its vitality and power. It is also believed that calcium supplements are detrimental to our health and that it is it better to gain calcium through our diet.

The *polycrest* plant for the detoxification and decalcification of the pineal gland is ***Passion Flower – Passiflora Incarnata (bud of flowers)*** 1:10, 15 gtts tid, QD. It may take six months to a year to decalcify.

If caused by fluoride (all pineal glands that are calcified have too much fluoride), the following plants are best:

Black Poplar – Populus Nigra (bud of leaves) 1:10, 15 gtts, tid, QD. Black Poplar is the most important contributor to “mineral homeostasis." It will selectively only secrete, chelate, pool (sequestrant), and excrete out of the body toxic metals while keeping on-board essential minerals unscathed. It is nature’s perfect agent for the remediation of many toxic pollutants. When in doubt or when limited testing can be performed to identify the levels of suspect clinical presentation of toxicants, this is the plant to think of for general toxic metals and xenobiotic detoxification over a wide, broad spectrum.

Dog Rose – Rosa Canina (young shoots) 1:10, 15-25 gtts tid, QD is one of the most important plants for the detoxification of fluoride. Methyl-3-*O*-methyl gallate (M3OMG) is a rare natural product that showed promising *in vitro* antioxidant activities. In this study, the protective role of synthetic M3OMG against sodium fluoride (NaF)-induced oxidative stress in rat brain was evaluated. Animals were treated with either M3OMG (10 and 20 mg/kg i.p.), vitamin C (10 mg/kg i.p.) as the standard antioxidant, or the vehicle (5% dimethyl sulfoxide; 1 ml/kg) for 1 week. Oxidative stress was induced in the brain by adding 600 ppm NaF in the drinking water for 7 days. At the end of the treatment period, the levels of thiobarbituric acid reactive substances (TBARS), reduced glutathione, and the activities of antioxidant enzymes (superoxide dismutase and catalase) were evaluated in brain homogenates. M3OMG treatment mitigated the NaF-induced oxidative stress through normalization of the level of TBARS, reduced levels of glutathione, and by the restoration of the diminished antioxidant enzyme activities. In conclusion, M3OMG could have a potential for treating ***neurotoxicity induced by fluoride*** or ***related environmental pollutants*** (Nabavi et al., 2013). Furthermore, it protects against all sorts of diseases caused by fluoride toxicity, including cardiotoxicity (Nabavi et al., 2012).

Judas Tree – Cercis Siliquastrum (bud of leaves) 1:10, adult dose 15 gtts tid, QD, will chelate and detoxify excess copper, lead, and silver in addition to being one of the best plants in the ***detoxification of fluoride***. *Polycrest* plant to inhibit hypersecretors of estrogen caused by xenoestrogen exposure.

N,*N*-dimethyltryptamine (DMT) is a potent endogenous hallucinogen present in the brain of humans and other mammals but not necessarily produce by the pineal gland. Despite extensive research, its physiological role remains largely unknown. Recently, ***DMT has been found to activate the sigma-1 receptor (Sig-1R)***, an intracellular chaperone fulfilling an interface role between the ***endoplasmic reticulum (ER)*** and ***mitochondria***. It ensures the correct transmission of ER stress into the nucleus, resulting in the enhanced production of ***antistress*** and ***antioxidant proteins***. Due to this function, the activation of Sig-1R can mitigate the outcome of hypoxia or oxidative stress. In this paper, they aimed to test ***the hypothesis that DMT plays a neuroprotective role in the brain*** by ***activating the Sig-1R***. Here was tested whether DMT can mitigate hypoxic stress *in vitro* cultured human cortical neurons (derived from induced pluripotent stem cells, iPSCs), monocyte-derived macrophages (moMACs), and dendritic cells (moDCs). Results showed that ***DMT robustly increases the survival of these cell types in severe hypoxia*** (0.5% O2) ***through the Sig-1R***. Furthermore, this phenomenon is associated with the decreased expression and function of the alpha subunit of the hypoxia-inducible factor 1 (HIF-1), suggesting that DMT-mediated Sig-1R activation may alleviate hypoxia-induced cellular stress and increase survival in a HIF-1-independent manner. These results reveal ***a novel*** and ***important role of DMT in human cellular***

physiology. These researchers postulate that this compound may be endogenously generated in situations of stress, ameliorating the adverse effects of hypoxic/ischemic insult to the brain (Szabo et al., 2016).

In 1965, a German team of researchers announced that they had isolated DMT from human blood (Franzen & Gross, 1965). In 1972, it was found in the human brain tissue, and then subsequently found in human urine and in cerebrospinal fluid bathing the brain (Saavedra & Axelrod, 1972). Once the pathways by which the human body made DMT were discovered, DMT had become the first endogenous human psychedelic. 5-MeO-DMT was then subsequently found in the cerebrospinal fluid in 1977 and considered as a neuroregulatory agent (Christian et al., 1997) – literally, because DMT is an endogenous human compound and is present in hundreds if not thousands of plants and figuratively, because of its intriguing and compelling effects touch upon so many fundamental human concerns: ***consciousness*** and the ***brain***, ***dreams*** and ***dying***, ***imagination*** and ***reality***. However, it is controversial, and for these reasons DMT will never go away (Strassman, 2000).

Patients who are ***'night owls'*** have been shown ***having misaligned rhythms*** that ***responded best to taking low-dose melatonin in the afternoon*** or evening, while ***'morning bird'*** early-risers experienced the most antidepressant effects by taking a low dose of melatonin in the morning. This melatonin treatment did not cause drowsiness because the dose was lower than what is usually taken at bedtime to induce sleepiness. Thus, it seems that ***the primary function of the pineal gland is modulating sleep patterns***. Studies have revealed that *endogenous melatonin is correlated with the decrease in body temperature* that occurs during sleep. It has been suggested that a rapid decrease in core body temperature increases our chances of sleep onset, and may also make it easier to enter into a deeper stage of REM sleep. However, it has not been firmly established ***to what extent body temperature affects sleepiness itself,*** but mounting scientific evidence supports the notion. For example, having a naturally elevated body temperature may be linked to insomnia, just as in menopausal females reporting to be awakened by hot flashes. In addition, being too hot or too cold can dysregulate our internal body temperature, making it challenging to fall asleep or stay asleep. Moreover, exercising just before going to sleep, or too close to bedtime, also makes it difficult to fall asleep. This is believed to be because it raises our core body temperature, as well as increases heart rate.

Other substances have been detected in the pineal gland of mammals, including those associated with reproductive function, as well as hypothalamic and pituitary hormones. For example, experiments on rodents have shown that the duration of the melatonin signal, which depends on how long it's dark, conveys information that ***regulates reproductive activity***. The relationship between the pineal gland and reproduction has not been firmly elucidated as of yet. Nevertheless, administration of melatonin to human subjects has been shown to alter the levels of sex hormones and both males and females, and inhibit the motility of sperm in men.

Melatonin is also related to the cardiovascular system. During nighttime, when melatonin levels are highest, blood pressure, heart rate, and cardiac output are greatly reduced. This relationship is corroborated by the fact that when melatonin is administered during the daytime, there is also a decrease in heart rate.

Studies have demonstrated that if you suppress endogenous melatonin in mice, you will see a decrease in spleen and thymus activity, as well as in the production of antibodies (immune response) to antigens (foreign or toxic substances). This effect was reversed when melatonin was administered. High dose of melatonin also increased T-helper cell activity, recognizing antigens. There is also an increase in the production of interleukin 2 (IL-2) that regulates the activities of white blood cells (WBCs), which are responsible for immunity.

Researchers have suggested several ways by which melatonin influence the immune system, based on the detection of melatonin receptors in lymphoid organs, such as the spleen, thymus, and lymphatic system, and in lymphocytes. In addition, animal studies highlight that melatonin has oncostatic properties, meaning it can halt the spread of cancer.

So, while we still do not fully understand the complete role of the pineal gland and its functions, it is clear that it serves a critical function that does not necessarily include producing altered states. On the other hand, the gaps in our knowledge about this tiny endocrine gland – as well as the fact that some philosophers have attached supreme importance to it – has led to the question of whether or not it does something far more mind-altering than regulating sleep. Strassman speculates that many mystical states might arise due to the endogenous production of DMT in the pineal gland.

So far as we know, DMT has been detected in small quantities in human blood, plasma, urine and kidney, and lung tissue. It has been detected in higher concentrations in the cerebrospinal fluid, which is a clear, colorless fluid that surrounds the brain and spinal cord. It acts as a cushion for the brain, providing mechanical and immunological protection. But what is DMT doing in the human body? So far, research has shown that DMT modulates the immune responses under various conditions – blocking inflammation, for example.

However, the role of DMT in human consciousness is another matter. The particular kind of enzyme thought to be crucial for DMT production – indolethylamine *N*-methyltransferase (INMT) – ***has not yet been detected in human brain*** or in the pineal gland. On the other hand, DMT has been found in rabbit brain tissue, without the presence of INMT, so perhaps DMT can be produced without INMT. Moreover, one study provides evidence of INMT in primate pineal glands, which could potentially support Strassman's hypothesis. There are definitely some obstacles to overcome: studying the pineal gland in living organisms is tricky; DMT is rather difficult to detect and is a controlled substance in most countries.

In an article published in the journal Psychopharmacology, psychedelic researcher David E. Nichols says that ***there is no reason to believe that altered states of consciousness are a result of the pineal gland producing DMT***. He underscores that the pineal gland weighs less than 0.2 grams and ***produces 30 ug (micrograms) of melatonin per day***. In order to induce a psychedelic experience, it would require producing about 25 mg of DMT. As a "rational scientist," Nichols argues that it is "simply impossible" for this tiny gland to "accomplish such a heroic biochemical feat." Also, since DMT is quickly broken down by MAO, there is no evidence it can accumulate within the

brain. Nichols believes we can explain out-of-body experiences and other altered states in other, more rational ways (Woolfe, 2017).

MEP™ Source of Phytomelatonin

Bramble – Rubus Fruticosus (young shoots) 805 pg/g = 0.000805 µg/g (Arnao, 2014).

Cowberry – Vaccinium Vitis-Idaea (young shoots) P ***22 mcg/g*** (Brown et al., 2012).

Fig – Ficus Carica (bud of leaves) 12,915 pg/g = 0.012915 µg/g or 12.9 ng/g (Zohar et al., 2011).

Grape Vine – Vitis Vinifera (bud of leaves) 965 pg/g = 0.000965 µg/g (Arnao, 2014), 3,000–***18,000 pg/g*** (Vitalini et al., 2011).

Linden Tree – Tilia Tomentosa (bud of leaves) 410 ng/g = 0.00041 mg/g (Gomez et al., 2015).

Maize – Zea Mays (germinating seeds) 2034 ng/g = 0.002034 mg/g, and 1,366 pg/g = 0.001366 (Hattori et al., 1995; Jinying et al., 2009).

Olive – Olea Europaea (young shoots) 4,306 pg/g = 0.004306 µg/g (Zohar et al., 2011), ***50–119 pg/mL*** (Arnao, 2014).

Raspberry – Rubus Idaeus (young shoots) 387 ng/g = 0.000387 mg/g (Chen et al., 2003).

Sour Cherries Montmorency – Prunus Cerasus (bud of leaves) P 13.46 ng/g = 0.00001346 mg/g µg/g (Burkhardt et al., 2001), ***39,000*** pg/g = 0.039 µg/g (Arnao, 2014).

St John's Wort – Hypericum Perforatum (bud of flowers) P 4490 ng/g = 0.00449 mg/g (Chen et al., 2003), ***1,8–23 µg/gL*** (Murch & Saxena, 2006), 2400-4000ng/g (Bhattacharjee & Dey, 2018).

Sweet Almond – Prunus Amygdalus (bud of leaves) P 1,400–11,260 pg/g = 0.0014 – 0.01126 µg/g (Arnao, 2014).

Walnut – Juglans Regia (bud of leaves) 3.5 ng/g = 0.0000035 mg/g (Reiter et al., 2005), 3,500 pg/g = 0.0035 µg/g (Arnao, 2014).

Wheatgrass – Triticum Aestivum (germinating seeds) P 124,700 pg/g = 0.1247 µg/g (Arnao, 2014; Hernandez-Ruiz et al., 2005).

Yarrow – Achillea Millefolium (young shoots) P ***340,000 pg/g*** = 0.34 µg/g (Arnao, 2014), ***43,000 ng/g*** (Conti et al., 2002).

Please note: Any of these plants when harvested at night will have ***at least two-fold more phytomelatonin*** than those reported by the above studies, which did not harvest these plants at the most opportune nocturnal or seasonal peak times. This perhaps explains why so many with a good level of melatonin in the pineal gland are reporting having vivid nightmares even with a small dose of Sour Cherries 15 drops. This is very telling that the amount of phytomelatonin may be as high as 10-fold that of what is reported for adult plant tissues. Furthermore, this could be attributed also, to the synergistic effects from whole plant total chemical composition. Another hypothesis is that EPEs and their high content of polyphenols, especially the sesquiterpenes are better at crossing the brain blood barrier. Whatever is the reason(s) EPEs in general appears to be a lot more effective than any synthetic or animal-derived melatonin source.

CLINICAL MANAGEMENT FOR INSOMNIA AND OTHER SLEEP DISORDERS with Embryonic Plant Extracts (EPEs)

Sleep REM PSC® Vegetable Embryonic Serum (VEG™) contains:

- California Poppy – Eschscholzia Californica (bud of leaves) 1:10
- Hops – Humulus Lupulus (bud of flowers) 1:10
- Passion Flower – Passiflora Incarnata (bud of flowers) 1:10
- Sour Cherries Montmorency – Prunus Cerasus (bud of leaves) 1:10

- Valerian – Valeriana Officinalis (embryonic roots) 1:10

It is a complex that contains not only Sour Cherries (phytomelatonin), but also other plants that serve to support a deep REM sleep. The dose greatly varies by individual: anywhere from 30-150 gtts taken into a little filtered water, 1½ to two hours before bedtime and within one hour of the exact same time every night, which is mandatory in achieving success in correcting long-standing insomnia. A person with chronic insomnia needs to: enter a pattern of regularity, stop all self-defeating root causes, and avoid all stimulants like coffee – even in the morning. Avoid bright light or loud music at night.

Sleep Alpha PSC® Vegetable Embryonic Serum (VEG™) contains:

- California Poppy – Eschscholzia Californica (bud of leaves) 1:10
- Hops – Humulus Lupulus (bud of flowers) 1:10
- Fig – Ficus Carica (bud of leaves) 1:10
- Linden Tree – Tilia Tomentosa (bud of leaves) 1:10

It is a complex that does not contain any phytomelatonin and is for less severe sleep problems that are definitely not related to low melatonin level.

A person with a long history of insomnia will need to work on this throughout the day by taking either Passion Flower – Passiflora Incarnata (bud of flowers) 1:10, 15 gtts tid, qid, PRN, QD, when having difficulty falling asleep due to too much chit-chat in the head at bedtime, or Valerian 1:10, 15-25 gtts tid, qid, PRN, QD. Sometimes both must be taken.

Interrupted sleep, regardless of cause, will be helped by taking California Poppy – Eschscholzia Californica (bud of leaves) 1:10, 30 gtts every time you wake up during the night straight into the mouth followed by a good sip of filtered water. This must be done every single time a person awakens during the night, as only in this way can you eventually break the pattern and correct it. This plant is excellent for insomnia associated with Parkinson's disease and even helps reduce tremors. California Poppy is also effective for the grief, bereavement, and mourning associated with the death of a loved one. In this case, as often as required take 30 gtts into a little filtered water; it works really well in lifting and considerably reducing that deep-seated-in-the-chest sick and pitting feeling. This plant is also excellent when a person is afraid of going to sleep because they may die and never wake up again. Often, these individuals suffer from thanatophobia (fear of death), which can be quite debilitating, especially if they end up with long period of insomnia. All humans to some degree have a fear of death, but California Poppy is indicated when this fear is overpowering and all-consuming. In such cases, use *ad libitum* whatever amount is required to clinically manage and reduce symptoms.

When the interrupted sleep is due to peri or post menopause including andropause, often you will need to give pro-progesterone Chaste Tree – Vitex Agnus Castus 1:10 throughout the day at a dose of 15-25 gtts, tid, PRN, QD. Always evaluate the dosage based on response, as some could need less while others may need to exceed the recommended dose.

Without any supplements, we can all help increase our melatonin levels by not suppressing it with artificial lighting. Start dimming the lights in your home for two hours before bedtime. Avoid exposure to overhead lighting, fluorescent lights, and the glare from TV and computer screens. Yes, that includes the e-readers! While it is easier said

than done, it is perfectly doable and not the self-defeating decreasing of your own melatonin levels with bright light. However, if still unable to sleep, mood lights will at least reduce the amount of phytomelatonin, which is required to get the good night's sleep that is critical to feeling well rested and ready to go in the morning. Anyone not getting at least eight hours of quality sleep every night will eventually pay a big price: far-reaching health consequences like memory loss – severe cognitive decline, lowered immunity, accelerated aging and ultimately exhausted, more stress and never feeling well and/or too often stricken with illnesses.

In cases of extremely tenacious and chronic insomnia, you may need both complexes (Sleep REM PSC® and Sleep Alpha PSC®), as well as all of the single plants suggested above during the daytime. Interestingly, some will require and do best with ***only one single embryonic plant extract (EPE)*** and on occasion even a plant that is not listed here – like Linden Tree – Tilia Tomentosa (bud of leaves) 1:10, for example. Although such extracts may be found in both complexes, some do best taking them alone, while still others may do better taking Valerian – Valeriana Officinalis (embryonic roots) 1:10 during the day and a higher dose at night – even 200 drops short-term until clinically well-managed. However, such a high dose will not be required for too long but sufficiently until some degree of correction is obtained. A good indication that it is time to reduce the dose of Sour Cherries because corrective levels of melatonin in the brain have been reached is when repeated vivid nightmares occur; this tells us the levels of melatonin in the pineal gland are reaching saturation – they have been therapeutically corrected. At this point, do not abruptly discontinue but rather decrease the dose until no longer having nightmares, and when symptoms once again recur, once more reduce the dose until no longer required. Similarly, a great way to evaluate brain serotonin levels is when you give a patient Linden Tree and instead of calming them down, a paradoxical effect is noticed – they become more anxious telling you that the level of serotonin is NOT deficient. This is a very dependable method in the evaluation of the brain's adequate serotonin level.

A person afflicted with cardiovascular diseases and extremely preoccupied with a heart condition to the point of obsessively thinking about it may do best with Hawthorn – Crataegus Oxyacantha/ Monogyna (bud of leaves) 1:10 alone at a dose of 30-50 gtts, tid, qid, PRN, QD. Remember Hawthorn is dose dependent being *bipolar*/*biphasic*, meaning that a low dose of 5-15 gtts will increase blood pressure, whereas doses above 25 gtts will reduce hypertension – it is ***both a selective*** and ***reversible*** calcium-channel blocker and an ACE inhibitor. Even with hypotensive patients, it will never adversely lower the blood pressure to cause fainting when given in a dose of 15 gtts, tid. Only when given at a higher dose of 25+ gtts can this be encountered.

For alcoholics or alcohol-caused insomnia, it is best to treat with Hops – Humulus Lupulus (bud of flowers) 1:10, 25-150 gtts, PRN, QD, one dose – if this is not sufficient within 45 minutes, give one more dose, this time tripling the first dose.