Melatonin and Health Benefits

This article is separated into 5 sections, each of which can be individually downloaded. It is a 'work in progress' incorporating new information whenever time permits.

Section 3

Operation trauma to Wi-Fi

1. Introduction; Age-related biological changes and increased life span; Alcohol-induced damage; asthma; autism; behaviour; bladder; blood-brain barrier; blood flow; blood pressure; brain damage; burns; cancer; cardiovascular support; Central Nervous System (CNS) injuries and diseases; chemical; dementia

2. Depression, bipolar disorder and mood control; diabetes, diabetic retinopathy; DNA damage; drug dependency; drug interaction; eye problems; fibromyalgia; headaches; head injury; height; immune system effects; infertility; inflammatory conditions; Irritable Bowel Syndrome (IBS) and other gastric problems; kidneys; learning and memory; light at night; light pollution; liver damage; lung injury; malaria; menopause; metabolic disorders; mitochondrial dysfunction; mouth diseases; nerve damage; neurocognitive functions; Neurodegenerative diseases, such as Huntington's disease; neurodevelopmental disorders; nitric oxide interaction; obesity

3. Operation trauma; ovarian disease; pain relief; pancreatitis; Parkinson’s disease; plants; pregnancy and reproduction; radiation side effects; schizophrenia; sciatic nerve injury; scoliosis; skin effects; sleep, sleep apnoea; spinal cord injury; stress; stroke; testicular protection; thyroid; toxin protection; treatment side effect reduction; vaccinations; ventilator-induced lung injury; Wi-Fi

4. Melatonin suppressors: Alcohol; age; baby crying; cancer; chemicals; diet; weight; electromagnetic fields (EMFs), powerfrequency radiation; occupational radar exposure; radiofrequency radiation; light; light at night (LAN); light wavelength; smartphone; fracture risk

5. References – 467 references

Operation trauma

It was suggested (Marseglia 2015) that melatonin may have a role in premedication of adults and children, supporting anaesthesia.

Melatonin was found to reduce post-operative delirium in children, though it did not reduce pre-operative anxiety (Kain 2009).

Intra-abdominal adhesions are important postoperative complications following abdominal surgery. Melatonin significantly reduced adhesion formation (Ersoz 2009).

Preoperative oral melatonin administration decreased pain scores and tramadol consumption and enhanced sleep quality, sedation scores, and subjective analgesic efficacy during the postoperative period (Borazan 2010). Mowafi & Ismail (2008) found similar effects.

Ovarian disease

Melatonin could become an important medication for improving ovarian function and oocyte quality and open new opportunities for the management of several ovarian diseases (Tamura 2009).

Pain relief

A review of papers (Ambriz-Tututi 2009) investigating the role of melatonin in pain relief concluded that melatonin receptors could prove attractive targets for developing analgesic drugs, including for the more difficult to treat neuropathic pain states.

Melatonin showed a significant analgesic effect on inflammatory pain (Laste 2012).

Exogenous melatonin has been used effectively in the management of pain in medical conditions such as fibromyalgia, irritable bowel syndrome and migraine and cluster headache. Melatonin has been tried during surgical operating conditions and has been shown to enhance both preoperative and post-operative analgesia. Melatonin exerts these pain-relief actions by acting at both spinal cord and supraspinal levels (Srinivasan 2012).

Pancreatitis

Melatonin helped prevent oxidative damage in acute pancreatitis (Col 2010), and was found to promote the spontaneous regeneration process of pancreatic tissue (Sidhu 2010).

Parkinson's disease

Mack (2016) and Rodriguez (2007) suggested that the melatonin's antioxidant abilities may help reduce the severity of symptoms of Parkinson's disease which involves inflammation and free radical damage in the brain. These also include sleep and anxiety disorders, depression and memory dysfunction. Melatonin restores brain function in zebrafish suffering with Parkinson-like disease (Díaz-Casado 2016). Bassani (2014) also found that melatonin exerts neuroprotective and antidepressant-like effects in the rotenone model of PD.

The antioxidant activity of melatonin may reduce damage caused by some types of Parkinson's disease. A Ukrainian study (Talanov & Sahach 2008) found that melatonin blocked the mitochondrial pore openings in nerve cells, helping to prevent neurodegeneration.

Melatonin is selectively taken up by mitochondrial membranes, a function not shared by other antioxidants (Srinivasan 2011). It has thus emerged as a major potential therapeutic tool for treating neurodegenerative disorders such as Parkinson's disease or Alzheimer's disease, and for preventing the lethal effects of septic shock or ischaemia/reperfusion (I/R).

Plants

It was found (Chen 2009) that melatonin applied to seedlings stimulated root growth. There were significant windows of dose and seedling age, and had no effect or even an inhibitory effect when given outside these windows.

When melatonin was added to soils under drought conditions (Wang 2013), the resultant oxidative stress was eased and leaf senescence was delayed.

Melatonin increased the germination of cucumber seeds at lower temperatures (Posmyk 2009).

Pregnancy and reproduction

Human melatonin has an important influence on the female genital system. In fact, melatonin may influence production and action of steroids, modifying cellular signalization on the target tissue (Maganhin 2008). Coelho (2012) states that there is evidence that melatonin acts directly on the regulation of ovary function.

Melatonin treatment for infertile women increased fertilisation and pregnancy rates. It could become a new cure for infertility (Tamura 2013, Kim 2013). Melatonin administration to middle-aged female rats produced beneficial effects that extend the reproductive function of the ovary (Fernadez 2013).

Daytime melatonin levels in normal pregnancies are low. Night-time melatonin levels increase after 24 weeks gestation, with significantly high levels after 32 weeks. These values decrease to non-pregnant levels on the second day after birth. Night-time melatonin levels are even higher in twin pregnancies after 28 weeks gestation. Patients with severe preeclampsia had significantly lower melatonin levels than the women with mild preeclampsia or normal pregnancies after 32 weeks gestation (Nakamura 2001). Melatonin protects against oxidative damage in the placenta caused by restriction of blood flow. It could be useful in treating preeclampsia and possibly other clinical states involving excess free radical production, such as foetal growth restriction and foetal hypoxia (Okatani 2001**)**. Melatonin receptors are widespread in the embryo, foetus and placenta since early stages. There is solid evidence that melatonin is neuroprotective and has a positive effect on the outcome of pregnancies (Voiculescu 2014).

Melatonin, which crosses the placenta freely without being altered, appears to be essential for a successful pregnancy (Soliman 2015). It also seems to be involved in correcting the pathophysiology of complications during pregnancy including those due to abortion, pre-eclampsia and foetal brain damage (Tamura 2008).

Reiter (2014) after a review of the role of melatonin in pregnancy concluded 1) melatonin, of both pineal and placental origin, has essential functions in foetal maturation and placenta/uterine homoeostais; 2) circadian clock genes, which are components of all cells including those in the peripheral reproductive organs, have important roles in reproductive and organismal (foetal and maternal) physiology; 3) due to the potent antioxidant actions of melatonin, coupled with its virtual absence of toxicity, this indoleamine may have utility in the treatment of pre-eclampsia, intrauterine growth restriction, placental and foetal ischemia/reperfusion, etc. 4) the propensity

for parturition to occur at night may relate to the synergism between the nocturnal increase in melatonin and oxytocin.

Melatonin treatment in the early dry-off period improves the reproductive performance of dairy cattle, reducing the number of days open, repeat breeding syndrome and pregnancy loss (Garcia-Ispierto 2013).

In an experiment by Fujinoki (2008) melatonin was found to enhance sperm hyperactivation in hamsters, and du Plessis (2010) found that the application of melatonin showed a significantly higher percentage of motile progressive motile and rapid cells in human spermatozoa, through a direct or indirect effect on the antoxidant scavenging effect of NO. Melatonin was found to protect sperm DNA from damage by organophosphorous pesticides (Sarabia 2009).

Melatonin supplementation prevented oxidative damage in rat testes induced by RF EMFs (Meena 2014, Oksay 2014), or fomaldehyde (Ozen 2008).

Exposure to 16 hours of light per day, followed by melatonin treatment improved the semen characteristics of male goats, especially during the breeding season (Ramadan 2009).

Melatonin had beneficial effects on the *in vitro* development of 2-cell mouse embryos (Tian 2010). Whether this applies to human foetal development is unclear as mice can be quite different.

Despite treatment with therapeutic hypothermia, almost 50% of infants with neonatal encephalopathy still have adverse outcomes. Melatonin is a hormone involved in physiological processes that also has neuroprotective actions against hypoxic-ischaemic brain injury in animal models. In a study by Robertson (2013), plasma levels of melatonin were 10,000 times higher in the hypothermia plus melatonin than hypothermia alone group.

Radiation side effects

The small intestine is the most radiosensitive gastrointestinal organ and patients receiving radiotherapy directed to the abdomen or pelvis may develop radiation enteritis (Hussein 2008). Administration of melatonin prior to irradiation can protect against the destructive effects of X-rays (Manda 2007, Reiter 2008). Manda (2009) found that melatonin pretreatment combated the delayed side effects of cranial radiotherapy. Shirazi (2007) suggested not only that melatonin was useful in helping prevent accidental damage to cells in proximity to target cells, but that it may be a useful radioprotector for radiation workers. Yildirim (2008) reported that pretreatment with melatonin prevented the damage that develops in CNS following irradiation.

Vijayalaxmi, in a review of melatonin as a radioprotective agent (2004) concluded that it may have a use in protecting individuals from radiation terrorism.

Schizophrenia

Melatonin was found to be potentially useful in the treatment of some disorders characterised by sensorimotor gating deficits such as schizophrenia (Uzbay 2013).

Sciatic nerve injury

Melatonin stimulates peripheral nerve regeneration. The effect of melatonin on damaged nerves depends on the time of treatment and may be related to its circadian rhythm (Kaya 2013).

Scoliosis

Melatonin deficiency plays a role in the prognosis of idiopathic scoliosis (Machida 2009). The authors suggest that melatonin supplements may prevent the progression of scoliosis, especially in mild cases with less than a 35 degree curve.

Skin effects

Melatonin is a major skin protectant and its functions may impact on skin biology and pathology (Fischer 2008, 2013). It has also been found to reduce the effect of burns (Bekyarova 2009) and mobile phone radiation (Ayata 2004).

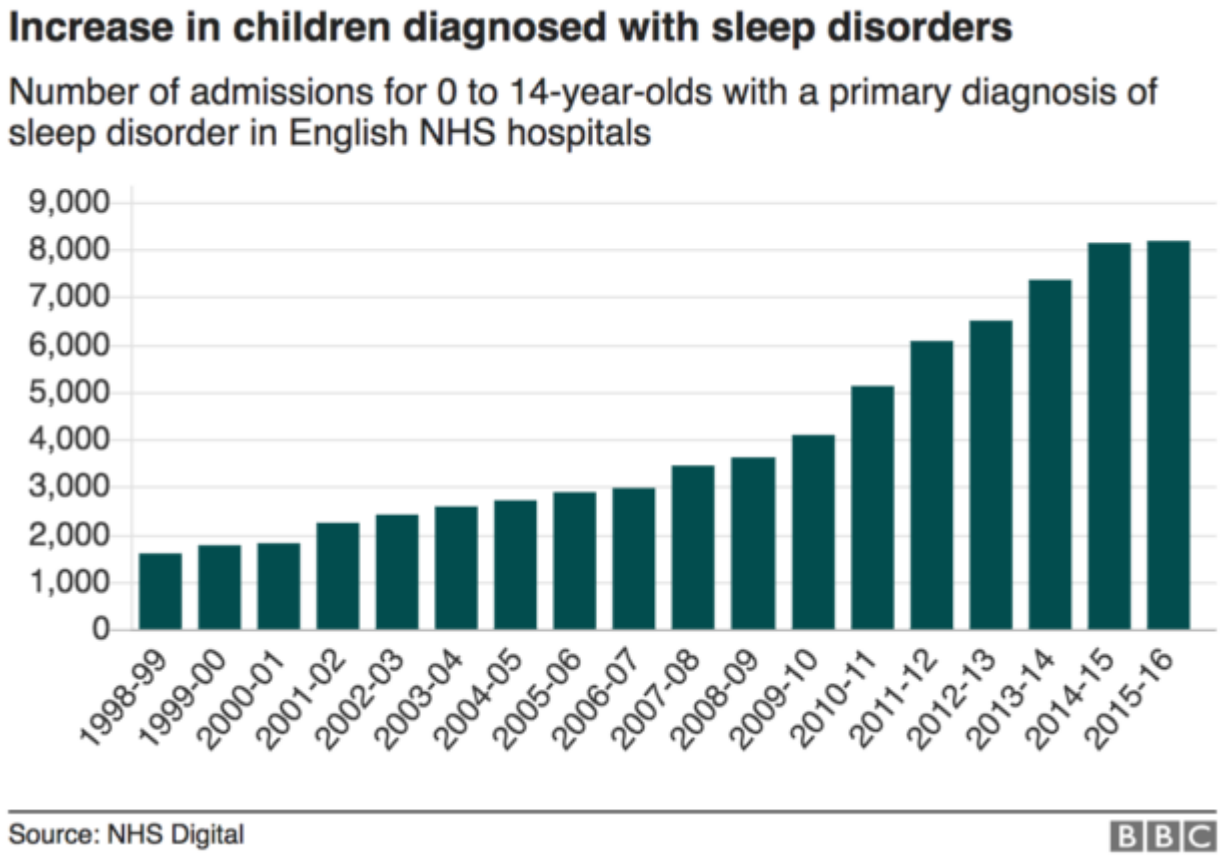
Melatonin has been found to protect skin cells against both UVA and UVB radiation (Izykowska 2009a, 2009b). Not only can melatonin protect against UV skin damage as it is a potent antioxidant, it can also stimulate the body's own protective system (Sierra 2013).

Melatonin treatment reduced the skin changes caused by 900 MHz radiation emitted by mobile phones (Ozguner 2004).

Skobowiat (2018) found that the exogenous application of melatonin or its derivatives represent a potent and promising tool for preventing UVB-induced oxidative stress and DNA damage.

Sleep

Hospital attendances in England for children under 14 with sleep disorders have tripled in 10 years, according to NHS data analysed by BBC Panorama. Sheffield Children's Hospital's sleep service has seen a tenfold increase in referrals over the past decade.



Poor sleep in children has been linked to a greater risk of obesity (especially in teenagers), lower immunity, mental health issues, lack of emotional control and poor school performance. Ten times more prescriptions of common sleep medication melatonin have also been written for children and adults under 55 over the same period.

One young person has a smartphone, two tablets and a television in her bedroom, and uses them just before bed. The Children's Sleep Charity has found 92% of the families using their specialist clinics had solved their child's sleep problems within six months by changing their bedtime routine. The charity says sleep problems are costing the NHS unnecessary millions in needless GP and paediatrician appointments and prescriptions (March 2017 The Guardian).

Circadian rhythm sleep disorders (CRSDs) include delayed sleep phase syndrome, advanced sleep phase syndrome, non-24 hour sleep-wake disorder, jet lag and shift-work sleep disorder. Disturbances in the circadian phase position of plasma melatonin levels have been documented in all these disorders (Pandi-Perumal 2008a). Raiewski (2012) found different regulation of melatonin secretion in different types of hamster, specifically the circadian control of the onset, offset and duration of nocturnal secretion, which may extend to differences within and between species, too. In a study on humans, circadian period varied between 23h 50 mins and 24h 31 mins ans correlated positively with the timing of the melatonin rhythm relative to habitual bedtime. The authors concluded that individual differences in circadian period and phase of the melatonin rhythm associate with differences in sleep, and suggest that individuals with a long circadian period may be at risk of developing sleep problems (Lazar 2013).

Mixed schedules of shift work produce the poorest sleep quality and seemed to disturb melatonin levels (Garde 2009). Melatonin therapy in shift workers with difficulty falling asleep significantly improved the sleep onset latency and sleep efficiency in a study by Sadeghniiat-Haghighi (2016). Melatonin secretion is suppressed by artificial light at night (ALAN). ALAN also results in sleep deprivation, and circadian disruption. Shift and/or night work generally decreases the time spent sleeping, and it disrupts the circadian time structure. In the long run, this desynchronization is detrimental to health (Touitou 2017).

The levels of melatonin in the body rise in the evening and this increase promotes the ability to fall asleep. Melatonin supplementation has been associated with an improved ability to get to sleep and also to stay asleep. This has long been known to sufferers of jet lag, who synchronise their body clocks by the judicious use of melatonin to re-assert proper sleeping habits. Melatonin was found to be an effective and well-tolerated treatment for insomnia in paediatric patients with Attention-Deficit/Hyperactive Disorder (ADHD) (Bendz & Scates 2010), autism and/or fragile X syndrome (Wirojanan 2009). Garzón (2009) found that melatonin significantly improved sleep and behavioural disorders in the elderly, and conventional drugs could be reduced. Melatonin supplementation helped alleviate sleep problems in people undergoing haemodialysis (Koch 2008).

The Food and Drug Administration in America has approved a drug containing melatonin and it is prescribed for the treatment of insomnia in children and the elderly (Reynoldson 2008). Any disruption in the quality of sleep with the accompanying cellular repair processes will clearly impact on many areas of health. Chronic sleep onset insomnia with late melatonin onset is prevalent in childhood, and has negative daytime consequences. Smits (2003) found that melatonin improves health status and advances the sleep-wake rhythm in children with idiopathic chronic sleep-onset insomnia. Melatonin treatment also significantly advanced sleep onset (van Maanen 2017, stronger effects than light treatment) by 57 minutes, sleep offset by 9 minutes, and melatonin onset by 82 minutes, and decreased sleep latency by 17 minutes. Lights-off time and total sleep time did not change. 90% children with chronic sleep initiation and sleep maintenance problems exhibited partial improvement up to a complete resolution of their sleep problems as measured by sleep latency time and number of awakenings reported by parents

(Ivanenko 2003). Thus, melatonin may be effective, safe, and well tolerated in the treatment of chronic insomnia in children.

A study by Eckerberg (2012) looking at teenagers, aged 14 – 19 years old, with sleep onset difficulties during school weeks found that melatonin helped. Reported sleep-onset times were advanced and sleep length was longer in the weeks they took melatonin. The students reported less wake up during the night, less school daytime sleepiness and increased evening sleepiness.

Melatonin is the most commonly prescribed medication for children's sleep disturbances by Australian paediatricians. 89% prescribed melatonin for poor sleep initiation (Heussler 2013).

In adults with chronic insomnia, long term treatment with a melatonin-based medication, ramelteon, reduced sleep onset time and promoted sleep with no residual effects, rebound insomnia or withdrawal symptoms upon discontinuation (Mayer 2009, Srinivasan 2009). Srinivasan suggested that melatonin promotes sleep by regulating the sleep/wake rhythm through the action on melatonin receptors in the suprachiasmatic nucleus (SCN). Wade & Downie (2008) suggested that melatonin significantly improved morning alertness and quality of sleep.

Synthetic melatonergic supplements primarily favour sleep initiation and reset the circadian clock to phases allowing persistent sleep, as required in circadian rhythm sleep disorders. A major obstacle for the use of melatonin to support sleep maintenance in primary insomnia results from its short half-life in the circulation. Solutions to this problem have been sought by developing prolonged release formulations of the natural hormone (Hardeland 2009).

Low nocturnal melatonin production and secretion have been documented in elderly insomniacs, and melatonin supplementation has been shown to be beneficial in treating sleep disturbances of these patients. It does not cause a hangover or withdrawal effects and is devoid of any addictive potential (Hardeland 2008, Zisapel 2009).

Intellectual disability is frequently associated with sleep disorders. It may be that the endogenous melatonin level may not be sufficient to adequately sat the sleep-wake cycles. Mutations in ASMT gene, involved in the production of melatonin, have been reported as a risk factor for autism spectrum disorder. Melatonin supplementation might be a valuable support in a subgroup of people with low melatonin synthesis (Pagan 2011).

Sleep is a thalamic function and it is assisted by melatonin which acts by promoting spindle formation. In this way, melatonin has a modulatory influence on sleep onset and maintenance (Jan 2009).

Melatonin supplements improved sleep patterns in an experiment where awareness of the time of day was withheld, and an artificial 20-hour day was imposed, and the normal melatonin secretion was out of phase (Wyatt 2006).

Sleep apnoea

Melatonin offers functional and metabolic protection in cases of intermittent hypoxia (IH), which is important to reduce pathological changes as a result of obstructive sleep apnea (OSA) (Bertuglia & Reiter 2009). Jain (2014) reported that sustained-release melatonin might improve sleep apnea.

Spinal cord injury

Melatonin was found to help following spinal cord injury, by reducing inflammation (Esposito 2009).

Stress

A melatonin-based antidepressant was found to block the adverse effects of stress on memory (Conboy 2009). Melatonin levels were found to be higher in children with acute stress (traumatic, surgical, psychic or febrile) or reduced in instances of chronic stress (Muñoz-Hoyos 2009). The authors concluded *"The lack of an appropriate response to acute stress could make some groups of patients predisposed to suffer depressive symptoms associated with a wide range of neurological, endocrinological or immunological consequences."*

Rapid melatonin consumption during elevated stress may serve as a protective mechanism of organisms in which melatonin is used as a first-line defensive molecule against oxidative damage (Tan 2007).

Melatonin has a specific role in mechanisms of consciousness, memory and stress and melatonin levels change under stressful conditions and in mental disorders (Bob 2008).

Wirtz (2008) found that melatonin helped reduce the risk of heart attacks following acute mental stress.

Stroke

Koh (2008a, 2008b) and Sung (2009) found that melatonin prevented cell death resulting from ischemic brain injury and suggested the most likely mechanism by which this was occurring. Wang X (2009) also demonstrated that melatonin, together with methazolamide was neuroprotective aganist cerebral ischemia, due to their ability to cross the blood-brain barrier and provide a mitochondrial-based screen. Ritzenthaler (2009) and Ahmad (2010) concluded that melatonin could have neuroprotective effects. Melatonin prevented vasospasm after subarachnoid hemorrhage (a type of stroke) and reduced arterial inflammation and oxidative stress (Fang 2009)..

Melatonin is both lipid- and water-soluble and readily crosses the blood-brain barrier. Increasing evidence has shown that, in animal stroke models, administering melatonin significantly reduces infarct volume, oedema, and oxidative damage and improves electrophysiological and behavioural performance. A paper by Lin & Lee (2009) reviewed studies that assess affects of melatonin on cerebral ischemia in acute, sub-acute and chronic stages. In addition to its potent antioxidant properties, melatonin exerts antiapoptotic, antexcitotoxic, ant-inflammatory effects and promotes mitochondrial functions in animals with cerebral ischemia. They concluded, given that melatonin shows almost no toxicity to humans and possesses multifaceted protective capacity against cerebral ischemia, it is valuable to consider using melatonin in clinical trials on patients suffering from stroke.

Elderly patients with delerium and insomnia after acute stroke were treated with a melatonin derivative. All patients had a significant improvement within a week, and nobody experienced oversedation, neurologic deterioration, or any other worsening effects (Ohta 2013).

Testicular protection

Pre-treatment and post-treatment with high-dose melatonin both significantly alleviated carbon ion-induced acute testicular damage, a greater radioprotective effect being observed in the pre-treatment group (Liu 2009). Yurtçu (2008) found that melatonin is a potent antioxidant agent in preventing testicular ischemia-reperfusion injury.

Thyroid

Melatonin is involved in a wide range of biological activities including antioxidant, oncostatic, anti-ageing and immunomodulatory properties. Although melatonin is synthesised mainly in the pineal gland, it is also synthesised in the thyroid (García-Marín 2012). Problems with the thyroid may well decrease production of melatonin.

Toxin Protection

Melatonin was found to protect against damage from formaldehyde-induced oxidative renal damage and neurotoxicity (Zararsiz 2007), tetrachloride-induced changes (Ogeturk 2004, Aranda 2010) arsenite-induced peripheral neuropathy (Lin 2009), deltamethrin (pesticide) induced nerve cell damage (Guo 2008), mitomycin C induced genotoxicity (Ortega-Gutiérrez (2009), benzene-induced lipid peroxidation in rat liver (Sharma & Rana 2010), 2-Bromopropaneinduced testicular toxicities (Huang 2009) and protected against mercury-exerted brain toxicity (Rao 2010). Alonso-Gonzalez (2008) found that melatonin helped prevent cancers that were a result of cadmium contamination, and El-Sokkary (2010) confirmed its antioxidant qualities in combatting cadmium toxicities. In a review of the effects of melatonin, Reiter (2008) found that it ameliorated the extensive free radical-mediated damage that ensued following exposure to a wide variety of environmental insults, including toxic prescription drugs, neural toxins, herbicides and metals.

Treatment side effect reduction

Melatonin can reduce some of the toxic effects associated with some chemotherapeutic agents and other carcinogens, acting both as an antioxidant-radical scavenger and a protective mechanism against cellular damage due to exposure to free radical-producing agents (Lialiaris 2008).

Vaccinations

The use of melatonin opens new perspectives for therapeutic manipulation of immune responses to vaccination (Regodón 2009).

Ventilator-induced lung injury

Melatonin decreases ventilator-induced lung injury by increasing the anti-inflammatory response in spite of an unexpected increase in oxidative stress (Pedreira 2008).

WiFi

Melatonin protected against oxidative stress caused by WiFi exposure (Aynali 2013).