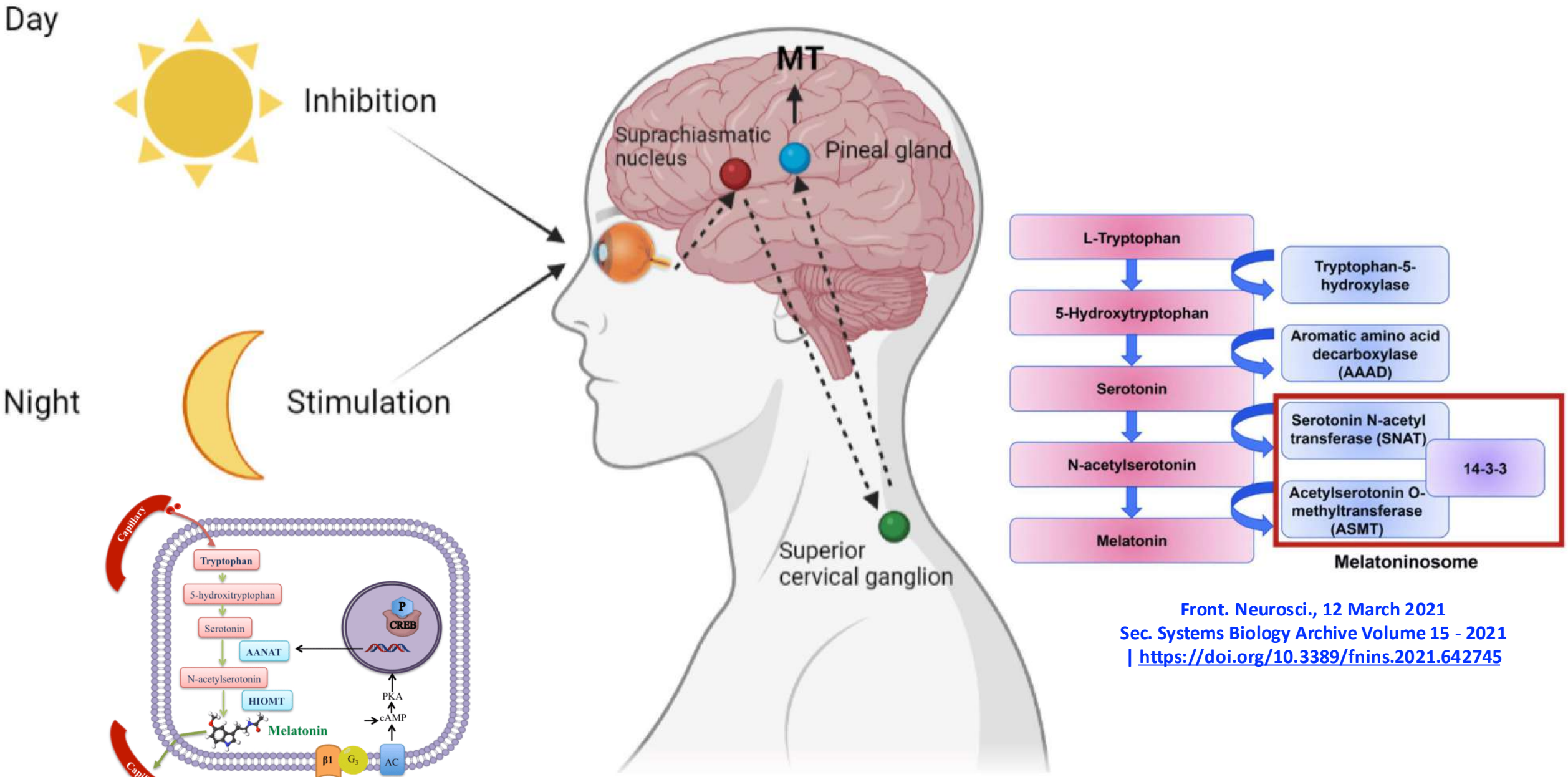
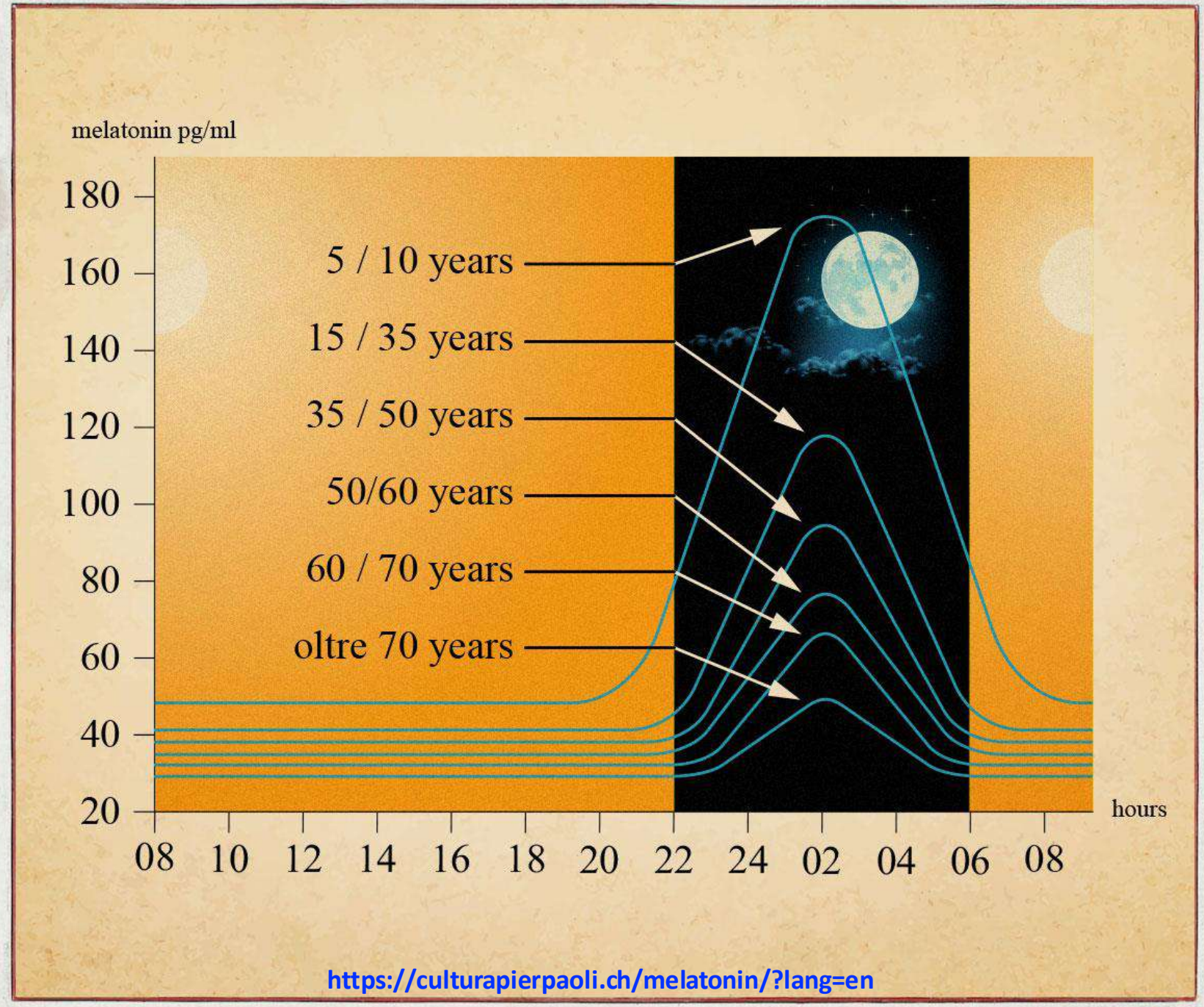
Melatonin a must in Aesthetic Medicine

Congress of the Belgian Society of Aesthetic Medicine April 26 and 27 2024



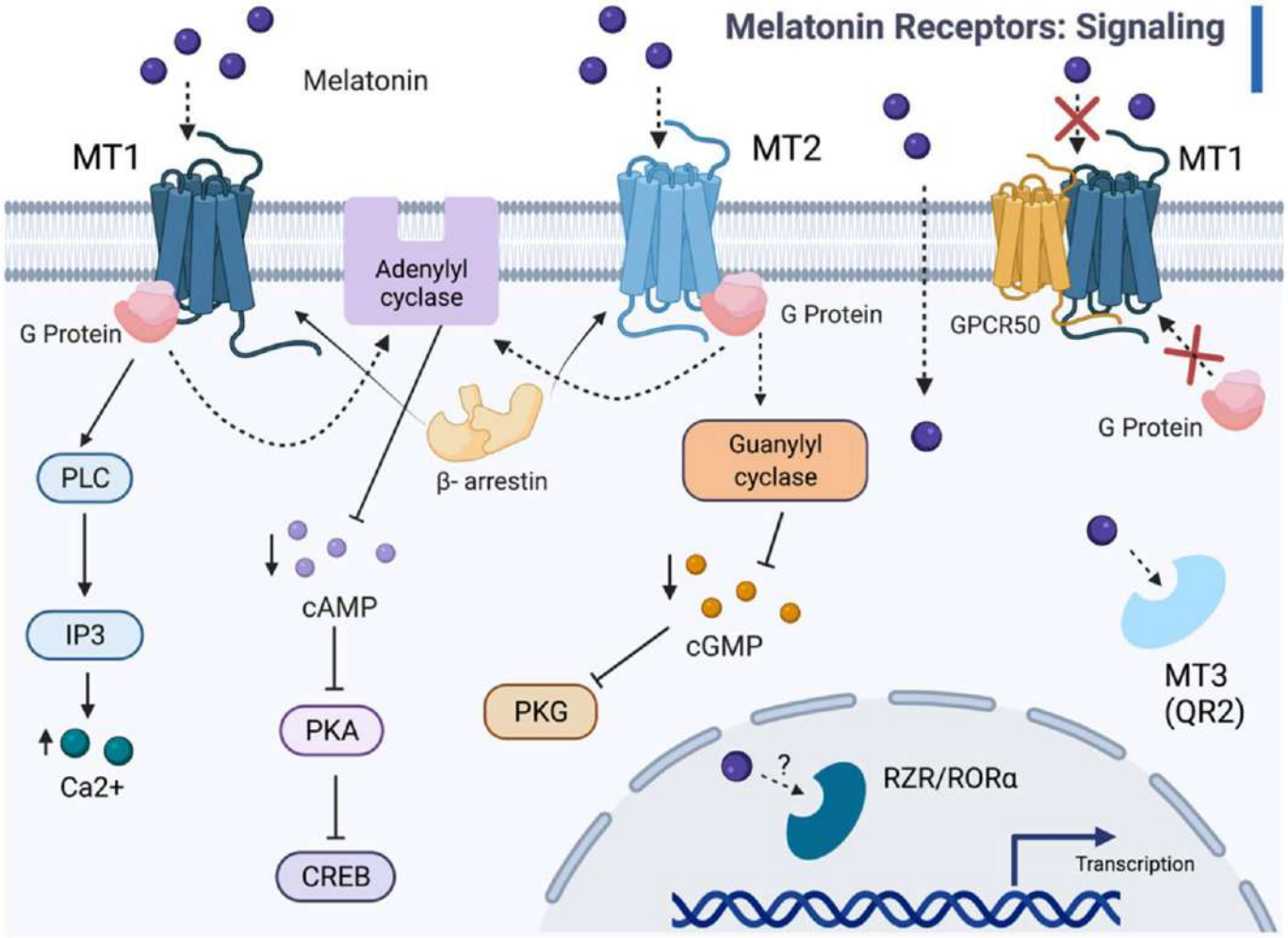
Front. Neurosci., 12 March 2021
Sec. Systems Biology Archive Volume 15 - 2021
| https://doi.org/10.3389/fnins.2021.642745

Melatonin as the Cornerstone of Neuroimmunoendocrinology. *Int. J. Mol. Sci.* 2022, *23*(3), 1835



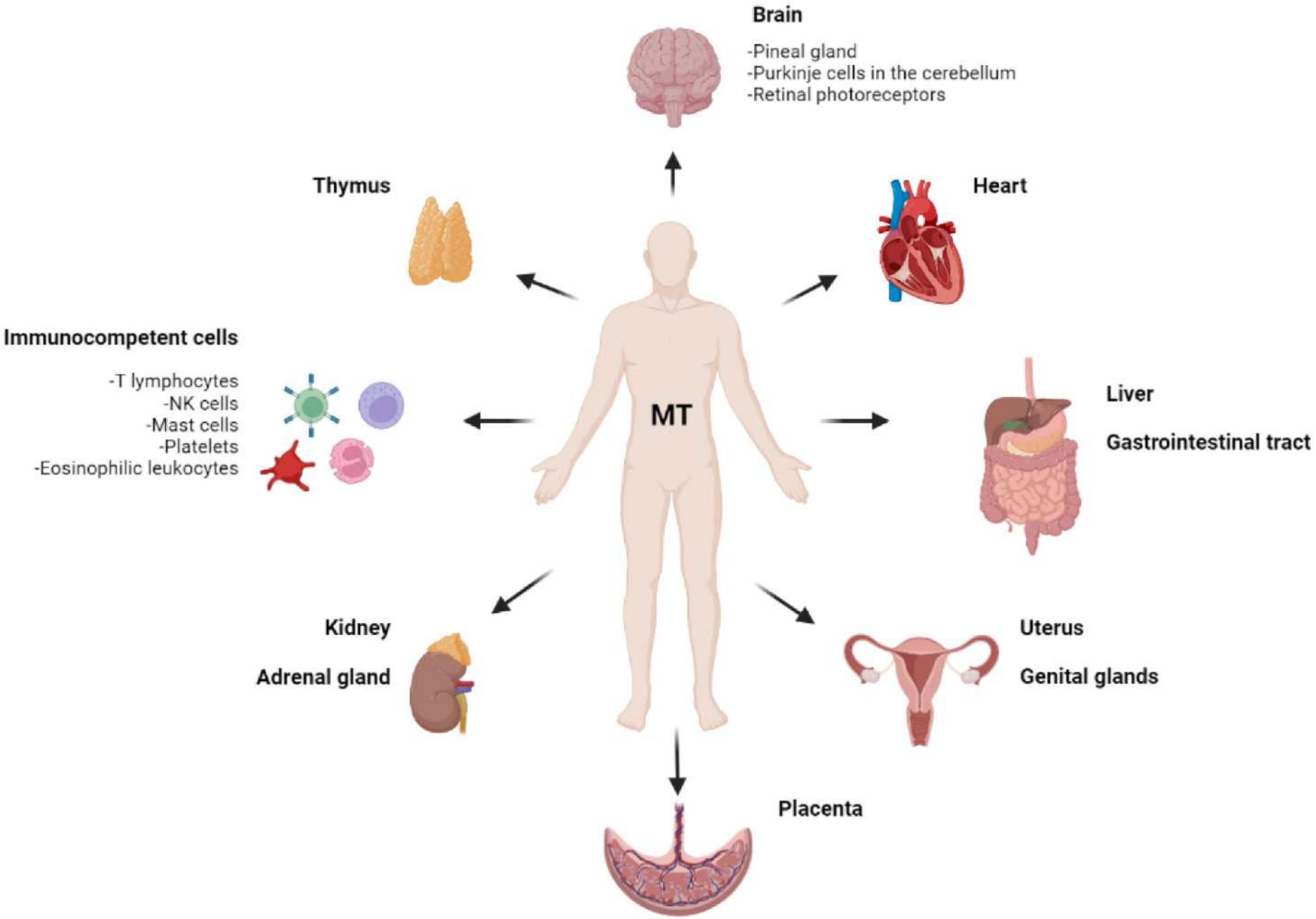
https://culturapierpaoli.ch/melatonin/?lang=en

The melatonin signaling cascades



The melatonin signaling cascades. Melatonin binds to transmembrane receptors MT1 and MT2, as well as the MT3 binding site on the cytosolic enzyme QR2, and, possibly, the nuclear receptor RZR/RORα.

Diseases 2021, *9*(4), 67; https://doi.org/10.3390/diseases9040067

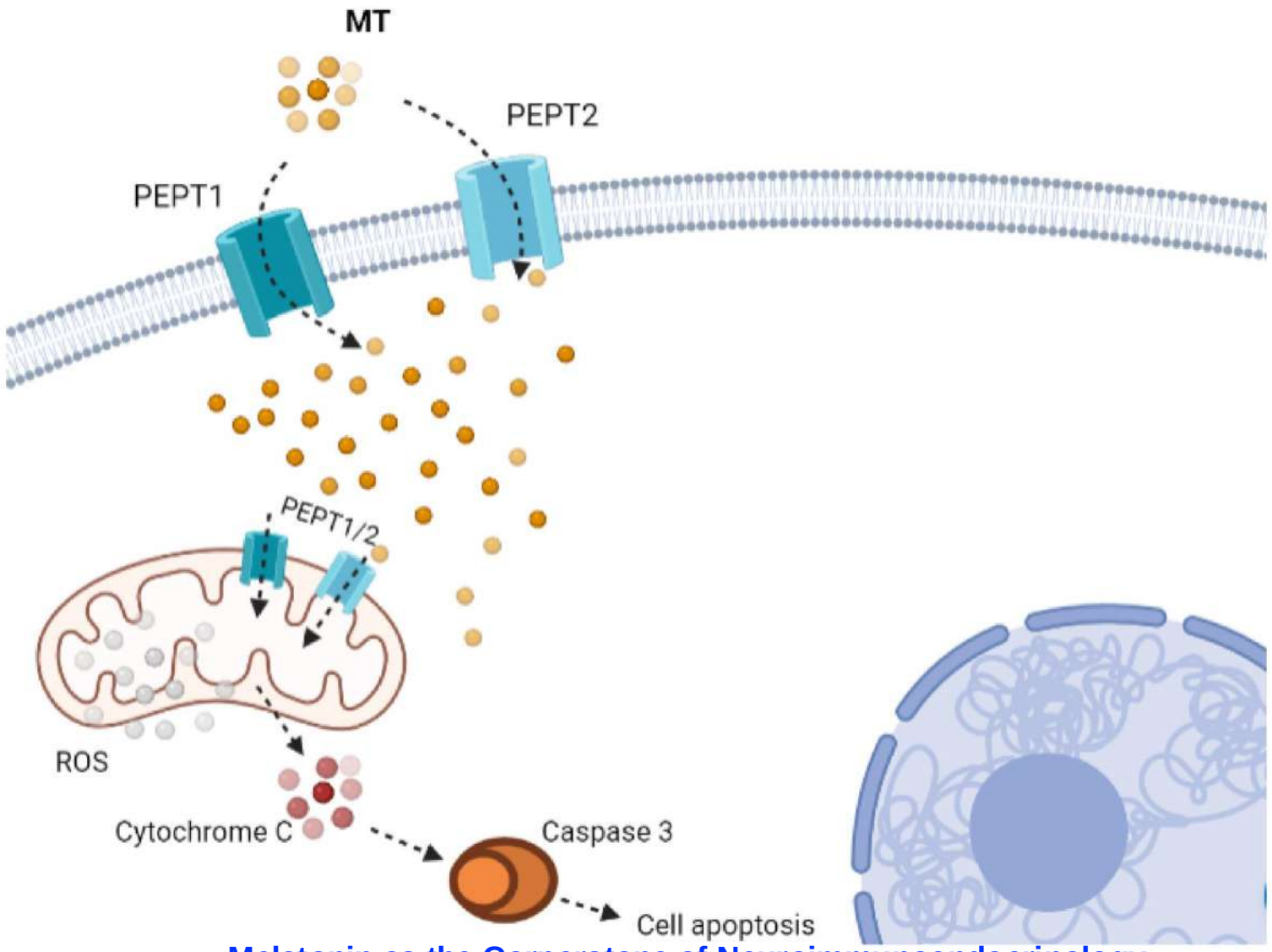


Melatonin is produced in oocyte mitochondria which give rise to all mitochondria in mammals.

The figure illustrates the unique property of melatonin to have the most widespread localization in the human body, being synthesized in various organs.

Melatonin as the Cornerstone of Neuroimmunoendocrinology. Igor Kvetnoy, Viktoria Polyakova and All. *Int. J. Mol. Sci.* **2022**, *23*(3), 1835; https://doi.org/10.3390/ijms23031835

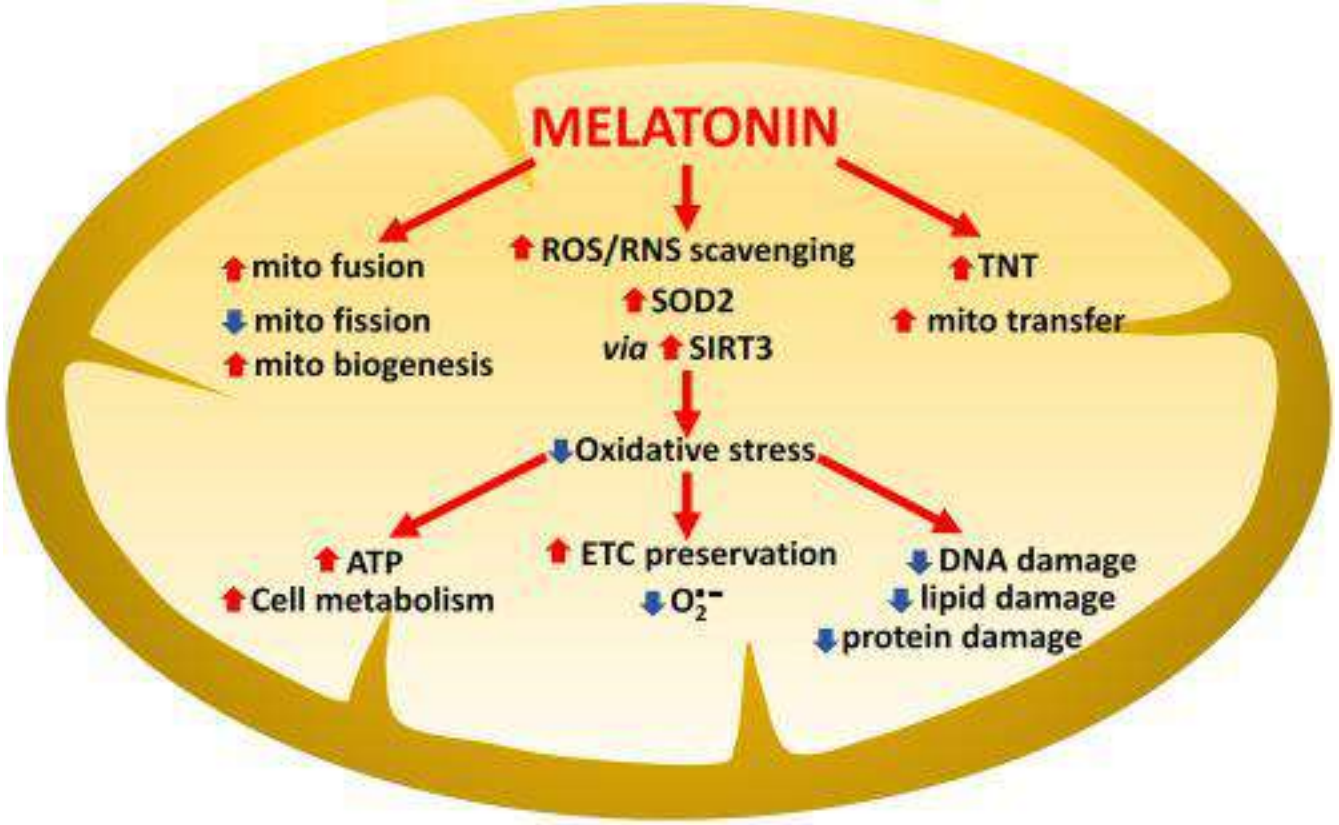
Melatonin and mitochondrial function



The high concentration of melatonin in mitochondria is due to the fact that PEPT1/2 proteins present in the mitochondrial membrane move melatonin into mitochondria against the gradient. Since melatonin is a powerful free radical scavenger, its presence in mitochondria reflects the participation of this hormone in compensatory reactions that occur during the development of mitochondrial aging and pathology associated with mitochondrial dysfunction

Melatonin as the Cornerstone of Neuroimmunoendocrinology. **Igor Kvetnoy, Viktoria Polyakova and All.** *Int. J. Mol. Sci.* **2022**, *23*(3), 1835; **https://doi.org/10.3390/ijms23031835**

Melatonin: A mitochondrial resident with a diverse skill set

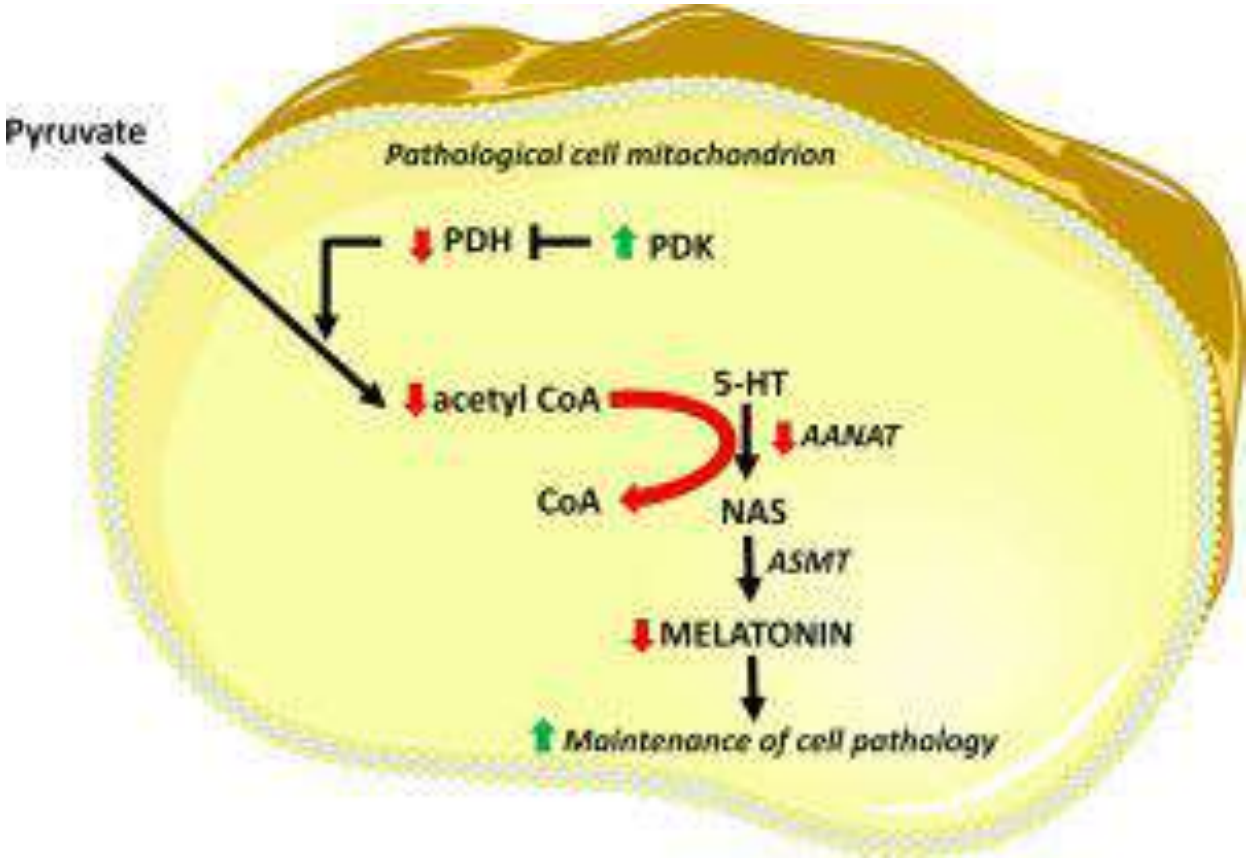


In recent years it has become apparent that melatonin is not only present in many tissues but is perhaps synthesized in the mitochondria of many cells and in the chloroplasts of chlorophyll-containing plants.

The findings of melatonin in these organelles as well as its likely synthesis at these sites are consistent with the earlier studies documenting the widespread organismal distribution of this multifunctional molecule. This is also in line with the proposed evolution of melatonin in prokaryotes which were subsequently phagocytized by primitive eukaryotes for their nutrient and energy generating value. The ingested melatonin-synthesizing prokaryotes evolved into mitochondria (α-proteobacteria) and chloroplasts (cyanobacteria) during which they retained their ability to produce the indoleamine. Since essentially all cells contain mitochondria (few exceptions), melatonin synthesis may be a universal process in all organs as suggested by recent findings.

Life Sciences Volume 301, 15 July 2022, 120612

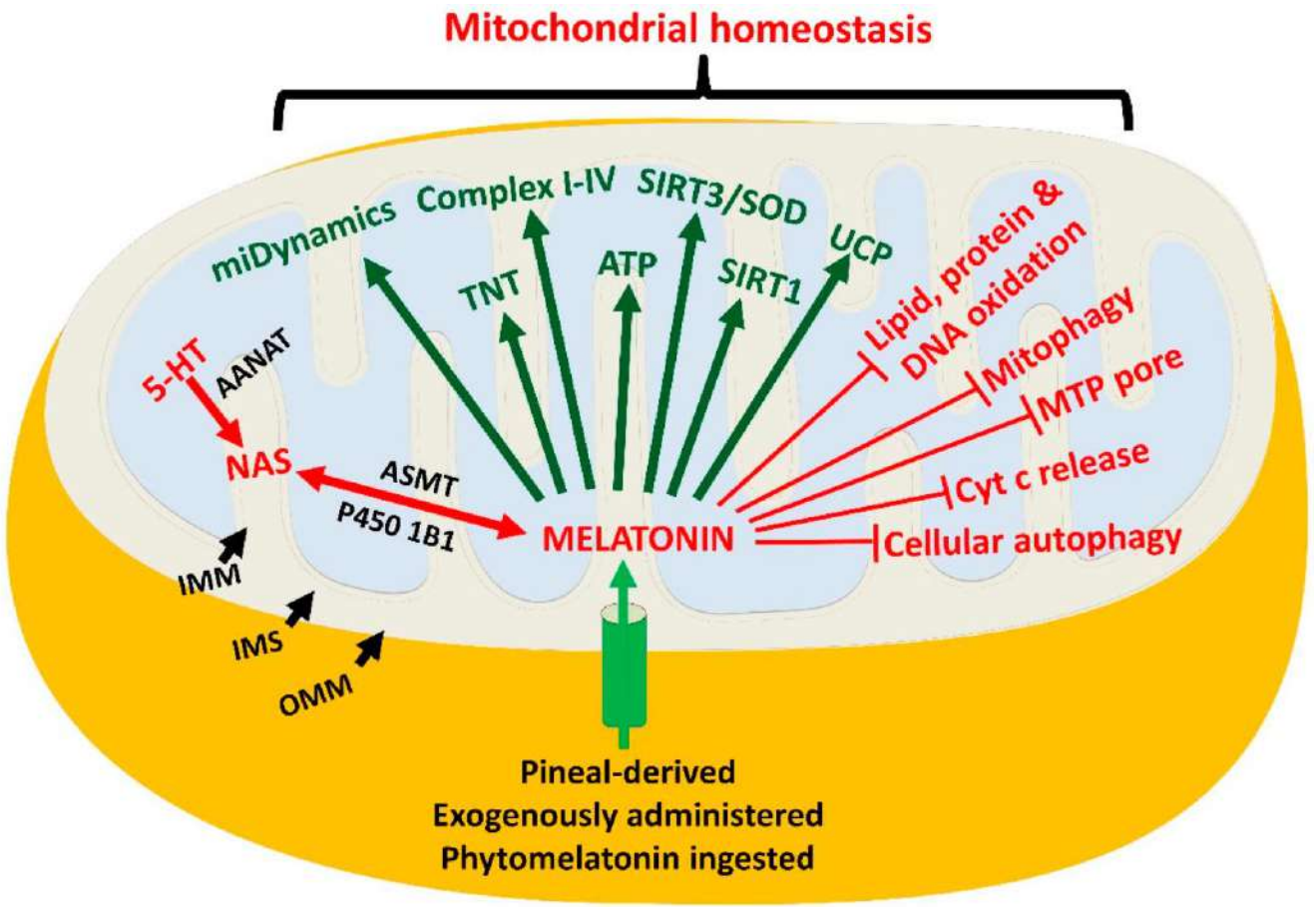
Melatonin: A mitochondrial resident with a diverse skill set



In addition to the requirement for the presence of serotonin in mitochondria for melatonin synthesis to occur, there is the need for an essential co-factor/co-substrate to assist with the conversion of serotonin to *N*-acetylserotonin. The necessary agent is acetyl-coenzyme A (acetyl-CoA), which is amply produced in mitochondria of healthy cells when pyruvate is decarboxylated by pyruvate dehydrogenase (PDH). In cells where pyruvate is significantly excluded from the mitochondria due to downregulation of PDH, acetyl-CoA may not be in sufficiently high concentrations to support ample melatonin synthesis in these mitochondria. Reduced mitochondrial acetyl-CoA production is presumably common in cells experiencing Warburg-type metabolism and in those suffering from low oxygen tension (hypoxia), etc. In the latter cells, PDH is suppressed due to the activation of pyruvate dehydrogenase kinase (PDK), a powerful inhibitor of PDH. While these mitochondria may have a reduced capability to produce their own melatonin, these organelles can still take it up from the circulation when it is available. Also, PDH suppression alone may not be adequate to totally eliminate melatonin synthesis in mitochondria since there are other routes of acetyl-CoA production in cells.

Life Sciences Volume 301, 15 July 2022, 120612

Representative actions of melatonin that involve the mitochondria



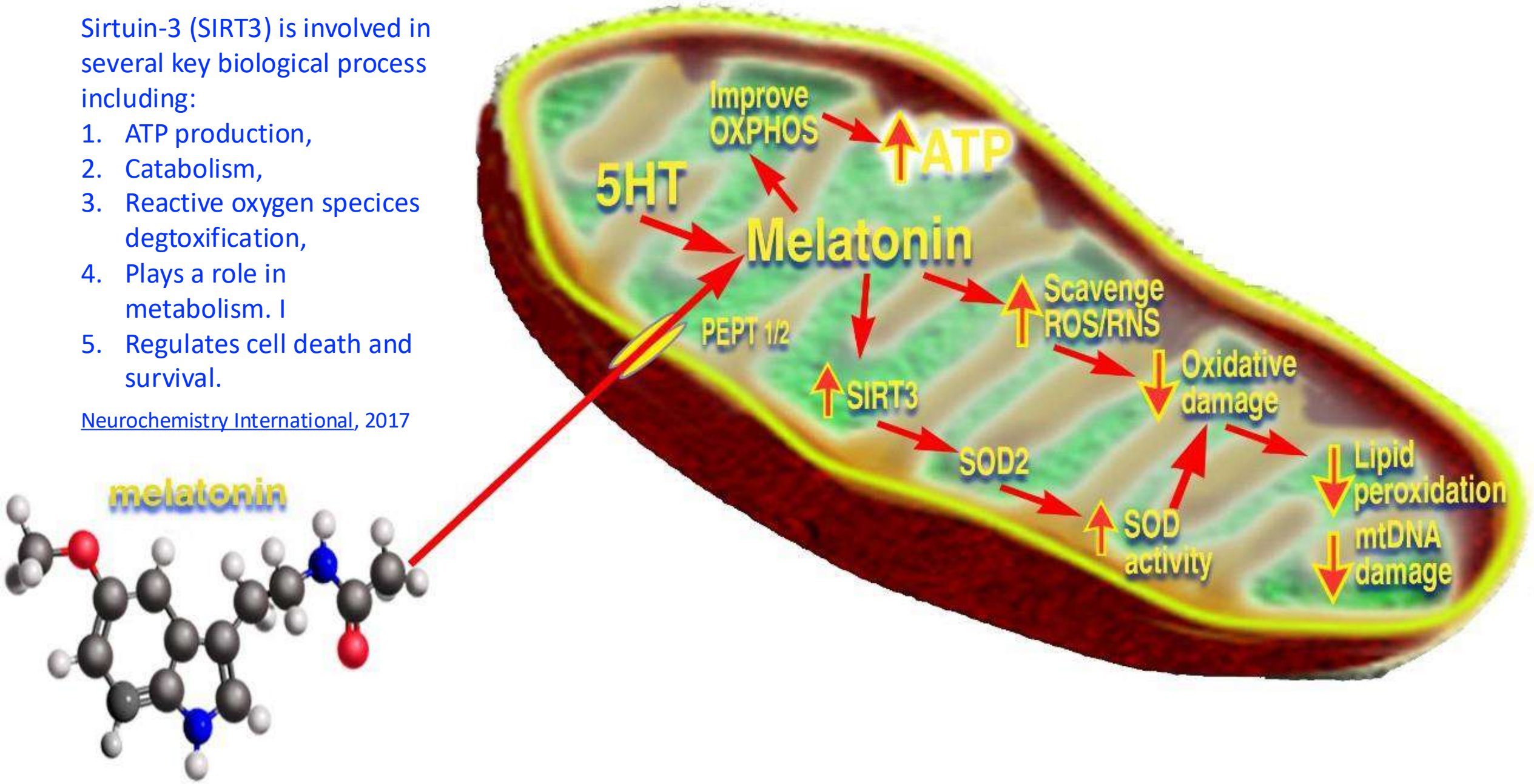
Melatonin, derived from the pineal gland, after supplemental ingestion or consumed in the diet is taken up by cells and transported into the mitochondria via the oligopeptide transporters, PEPT1/2. All cells are believed to synthesize melatonin in their mitochondria via the conventional pathway as described in the pineal gland. In mitochondria, melatonin can be reverse-metabolized to its precursor, N-acetylserotonin (NAS); this involves the extrahepatic monooxygenase enzyme, P450 1B1. Thus, the changes induced by melatonin may also involve NAS production. The most recently discovered actions of melatonin that involve the mitochondria are its effects on tunneling nanotubes (TNT) which allow for the transfer of mitochondria between cells. 5-HT = serotonin; AANAT = arylalkyl-N-acetyltransferase; ASMT = acetyl serotonin methyltransferase; Cyt c = cytochrome c; IMM = inner mitochondrial membrane; IMS = Intermembrane space; miDynamics = mitochondrial dynamics; MTP = Mitochondrial permeability transition pore; OMM = outer mitochondrial membrane; UCP = uncoupling protein; SOD = superoxide dismutase.

Melatonin and Pathological Cell Interactions: Mitochondrial Glucose Processing in Cancer Cells. I*nt. J. Mol. Sci.* 2021, *22*(22), 12494

Sirtuin-3 (SIRT3) is involved in several key biological process including:

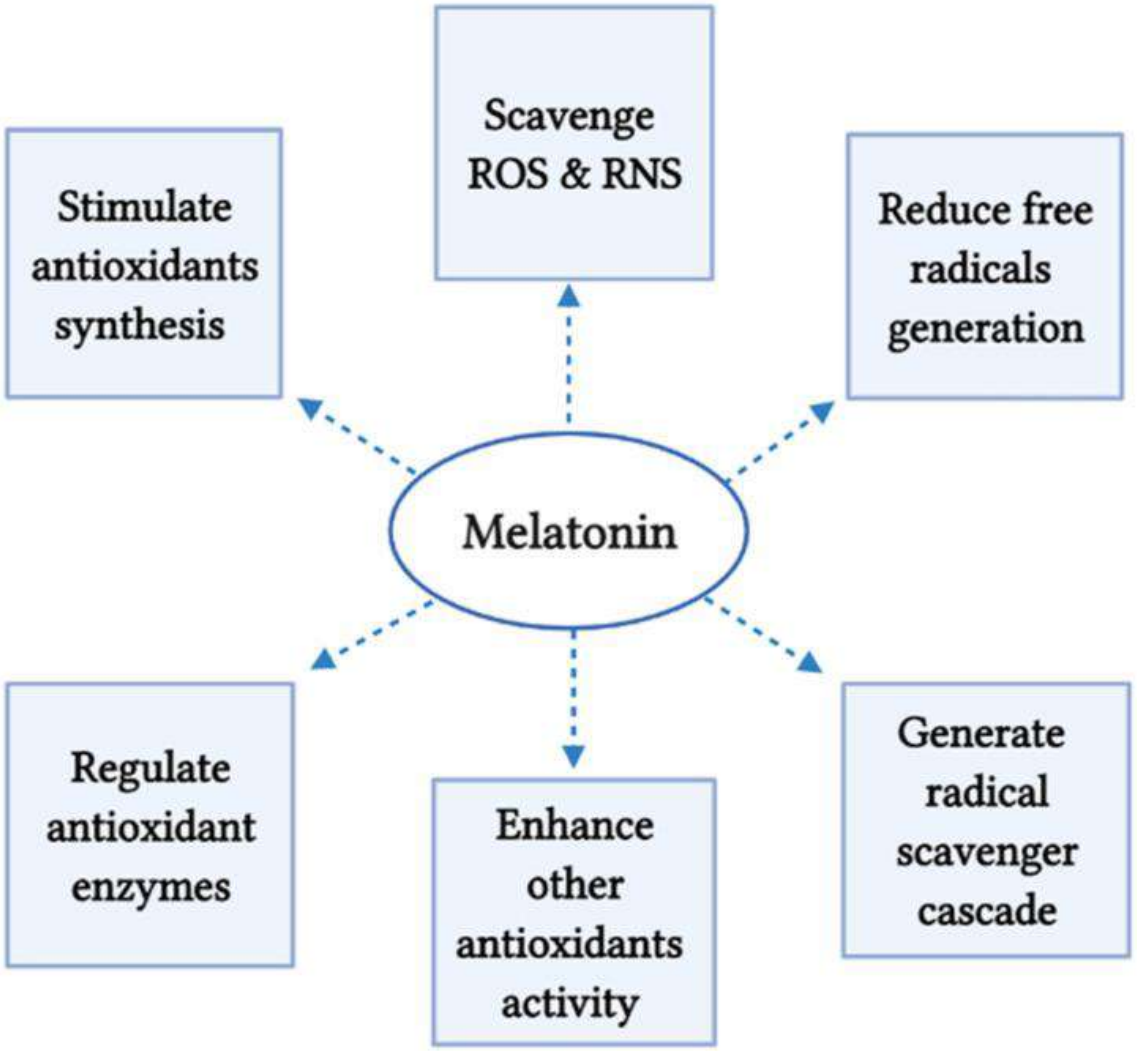
1. ATP production,
2. Catabolism,
3. Reactive oxygen specices degtoxification,
4. Plays a role in metabolism. I
5. Regulates cell death and survival.

Neurochemistry International, 2017



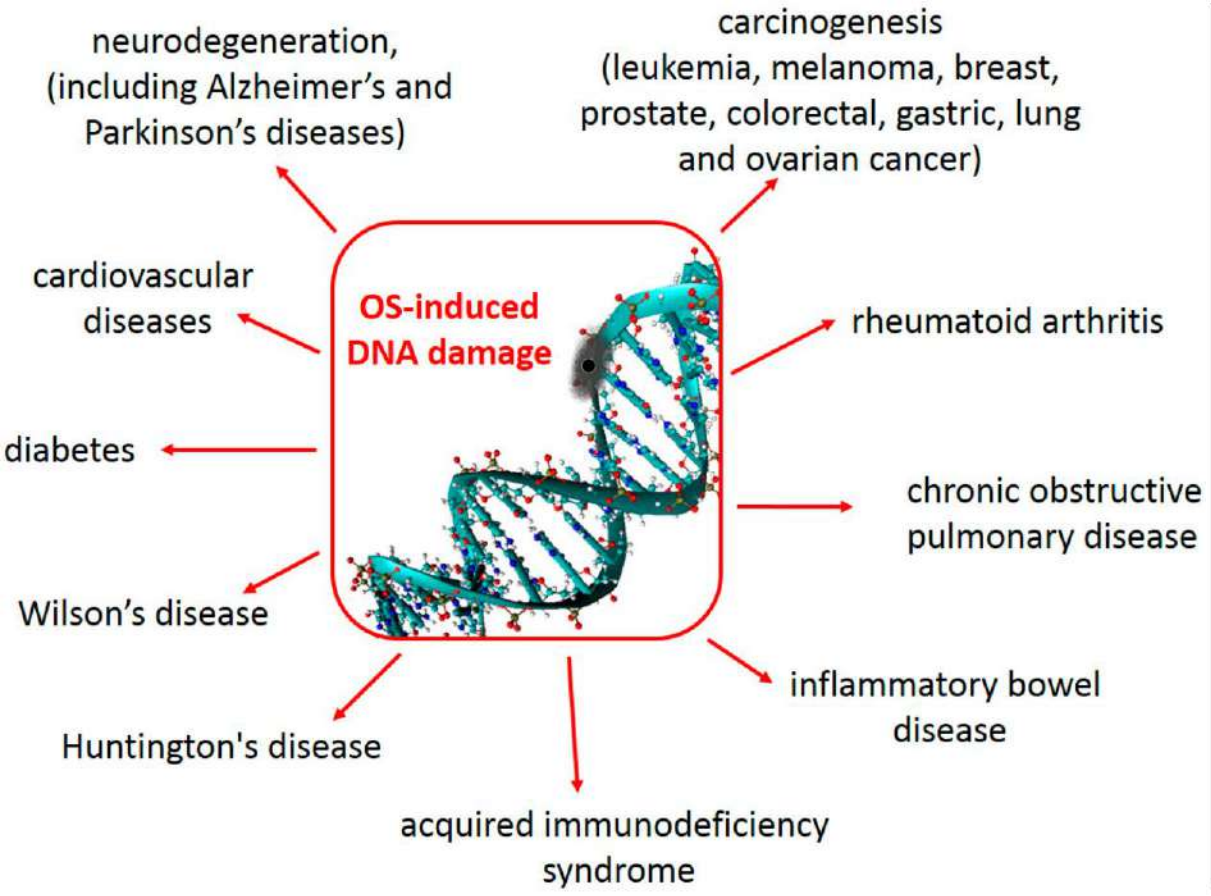
Melatonin Mitigates Mitochondrial Meltdown: Interactions with SIRT3. *Int. J. Mol. Sci.* 2018, *19*(8), 2439; https://doi.org/10.3390/ijms19082439

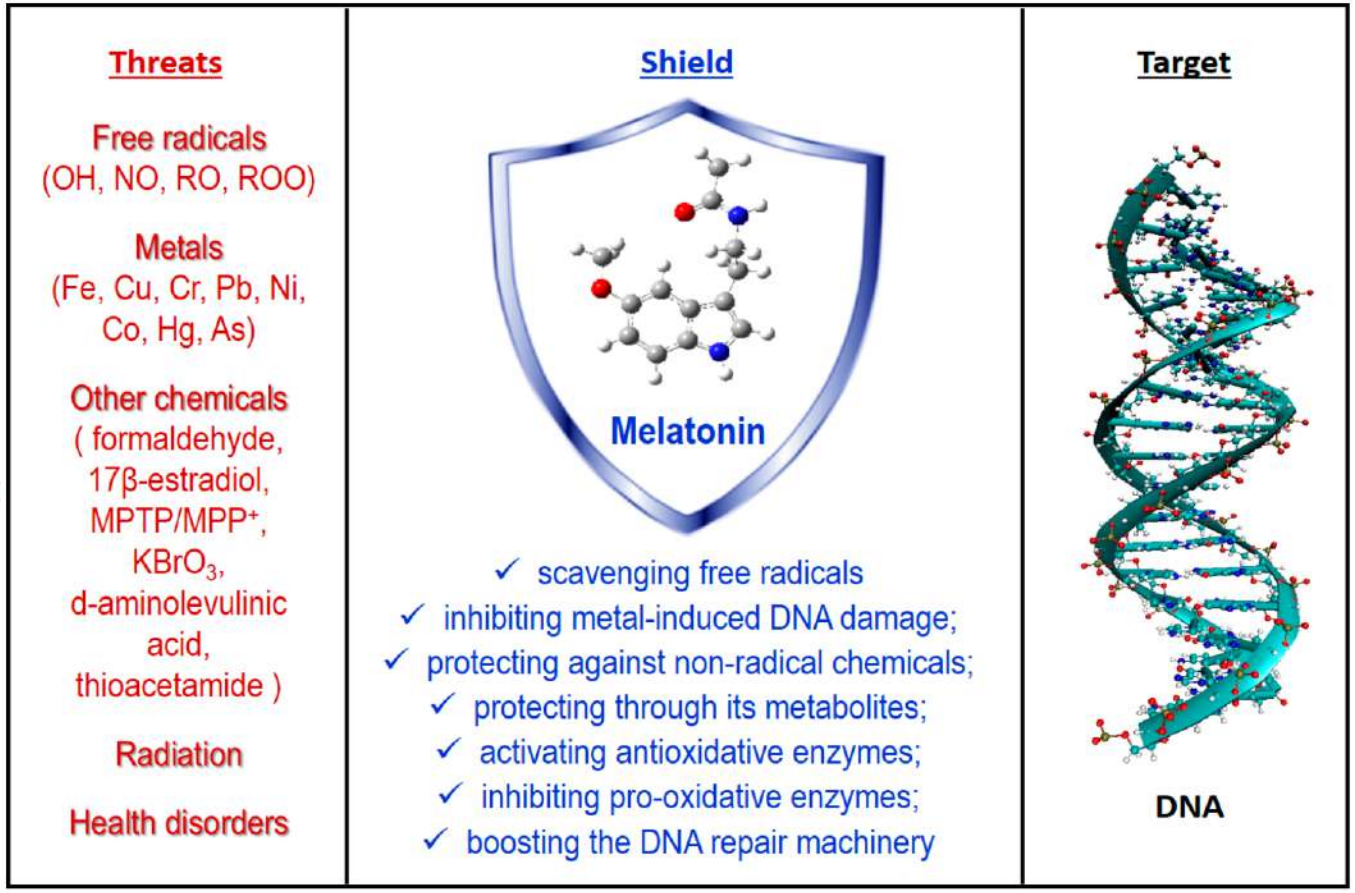
Melatonin's mechanisms as antioxidant. ROS, reactive oxygen species; RNS, reactive nitrogen species



Melatonin in Cancer Treatment: Current Knowledge and Future Opportunities. Molecules. 2021 May; 26(9): 2506

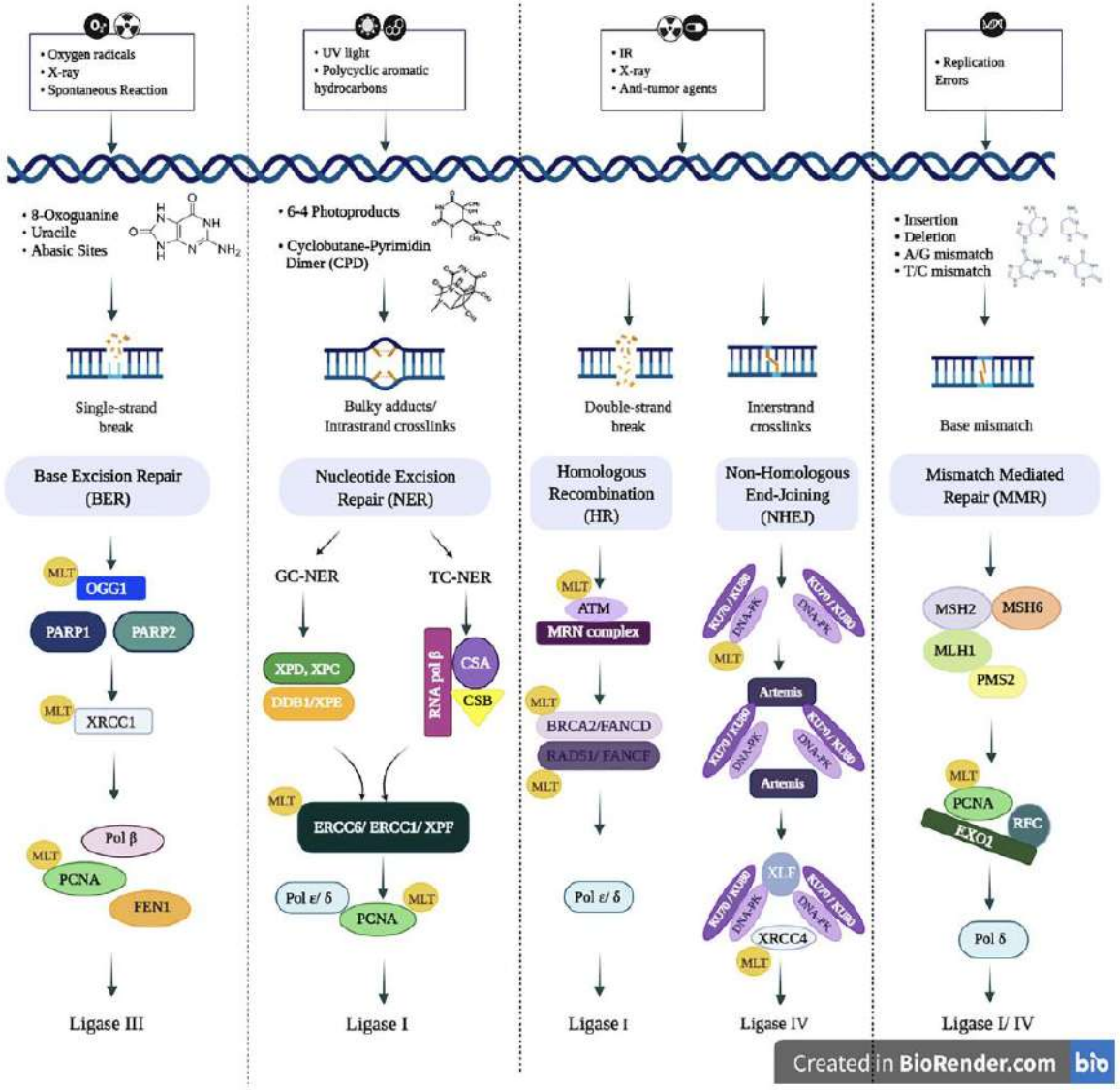
Melatonin: A Versatile Protector against Oxidative DNA Damage





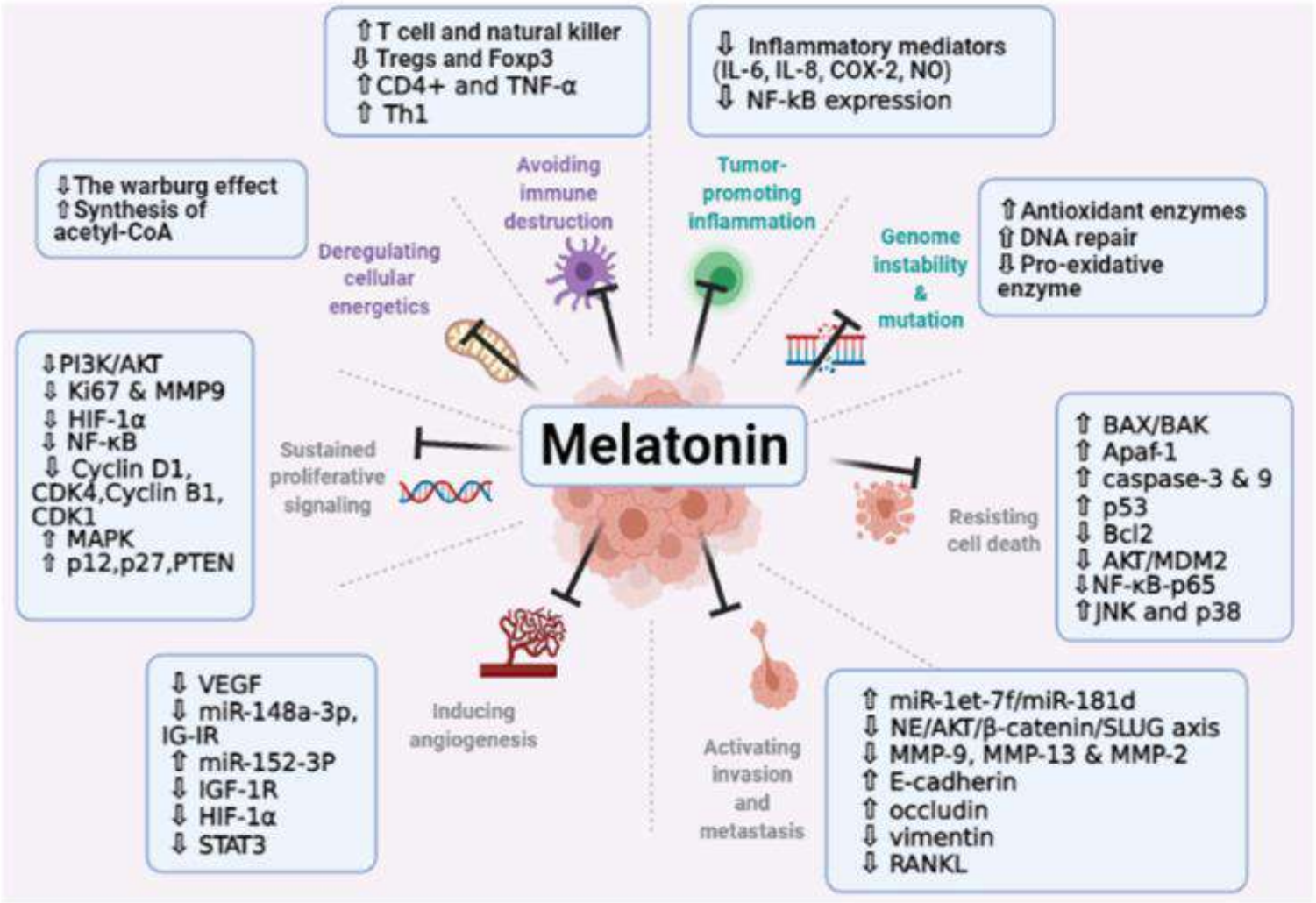
Molecules 2018, *23*(3), 530; https://doi.org/10.3390/molecules23030530

Melatonin: A smart molecule in the DNA repair system



Cell Biochem Funct. 2022 Jan;40(1):4-16. doi: 10.1002/cbf.3672. Epub 2021 Oct 21

Summary of melatonin activity in restraining cancer hallmarks



Melatonin showed to be safe for daily doses up to 100 mg/kg.

Based on human trials and reported use, melatonin seems to have a high safety profile especially when used in appropriate doses and short term. Although the doses used in the published studies are 10–50 mg/d higher than those used for other indications (0.5–5.0 mg/d), none of the studies found any severe adverse effects linked to melatonin; while, melatonin decreased some of the side effects caused from radiotherapy and chemotherapy.

According to a systematic review and meta-analysis of 21 clinical studies dealt with solid tumors, melatonin significantly reduced thrombocytopenia, leucopenia, asthenia, nausea, vomiting, and hypotension.

Melatonin in Cancer Treatment: Current Knowledge and Future Opportunities. Molecules. 2021 May; 26(9): 2506

Melatonin triggers p53Ser phosphorylation and prevents DNA damage accumulation

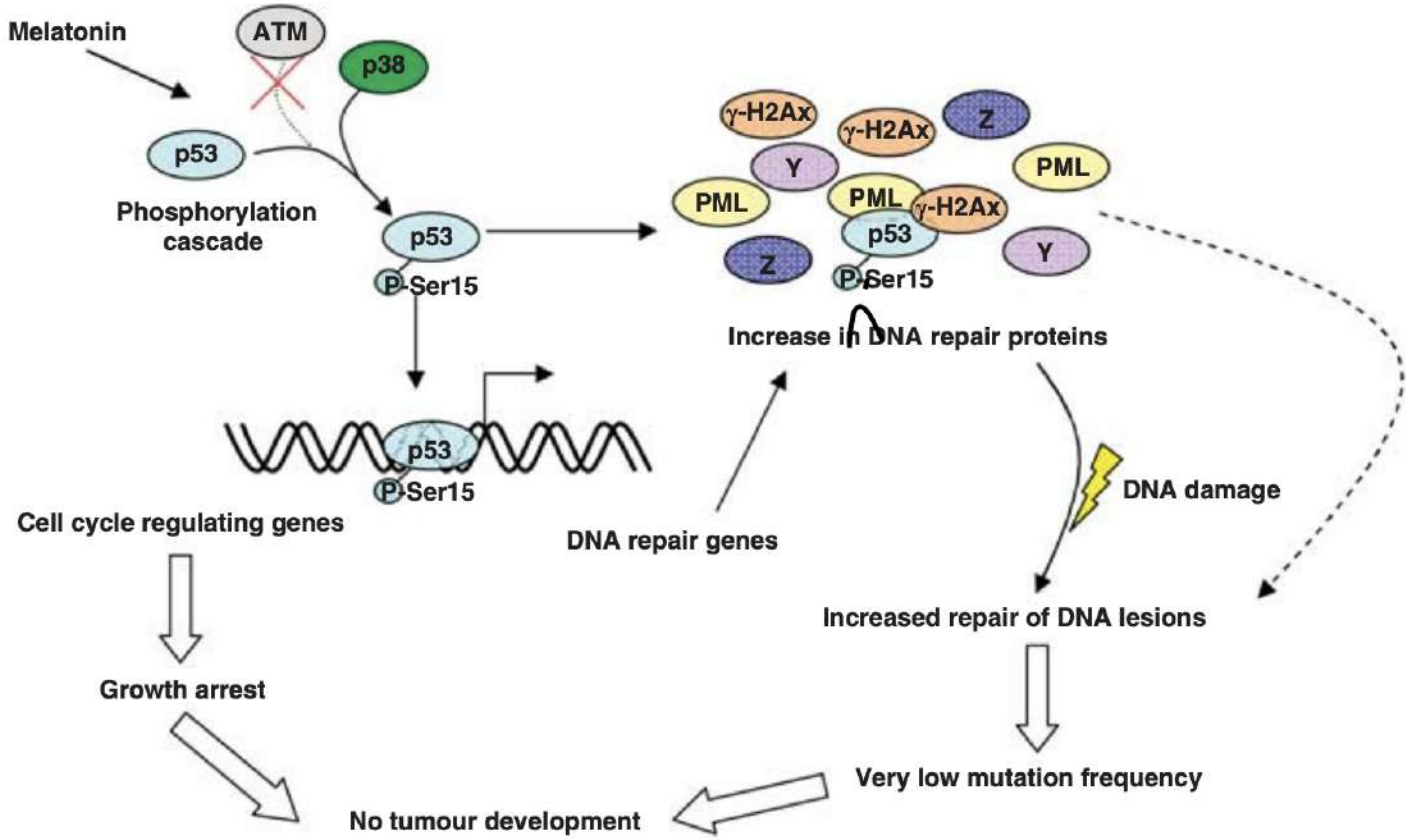
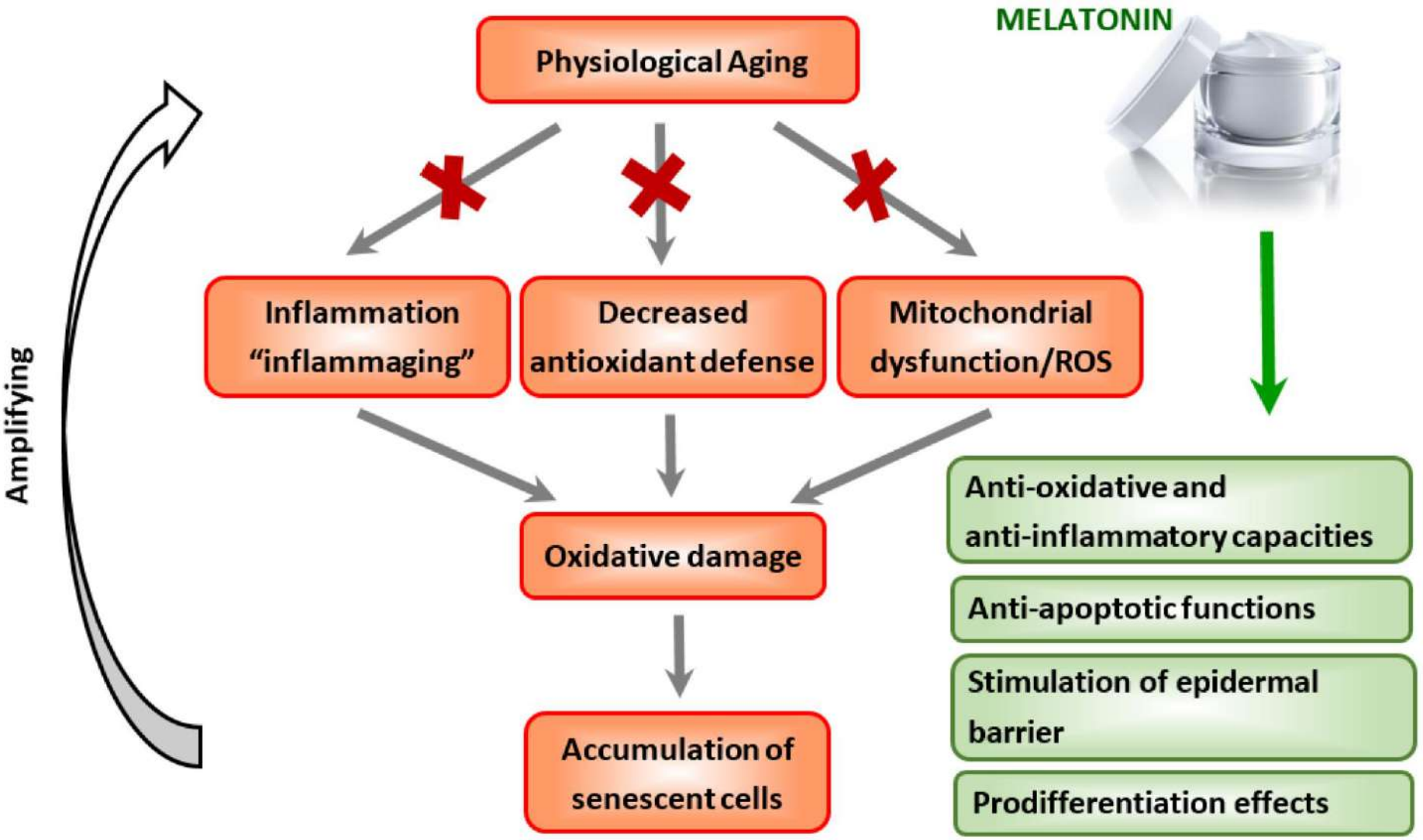


Figure 7 Model depicting melatonin's action. Melatonin treatment induces a p38-dependent phosphorylation cascade that activates p53 and other repair proteins. This translates in an increased ability of cells to detect DNA damage and repair it. This results in a lower mutation frequency.

Oncogene

Melatonin triggers p53^{Ser} phosphorylation and prevents DNA damage accumulation. R Santoro, M Marani, G Blandino, P Muti & S Strano. Nature *Oncogene* volume 31, pages2931–2942 (2012)

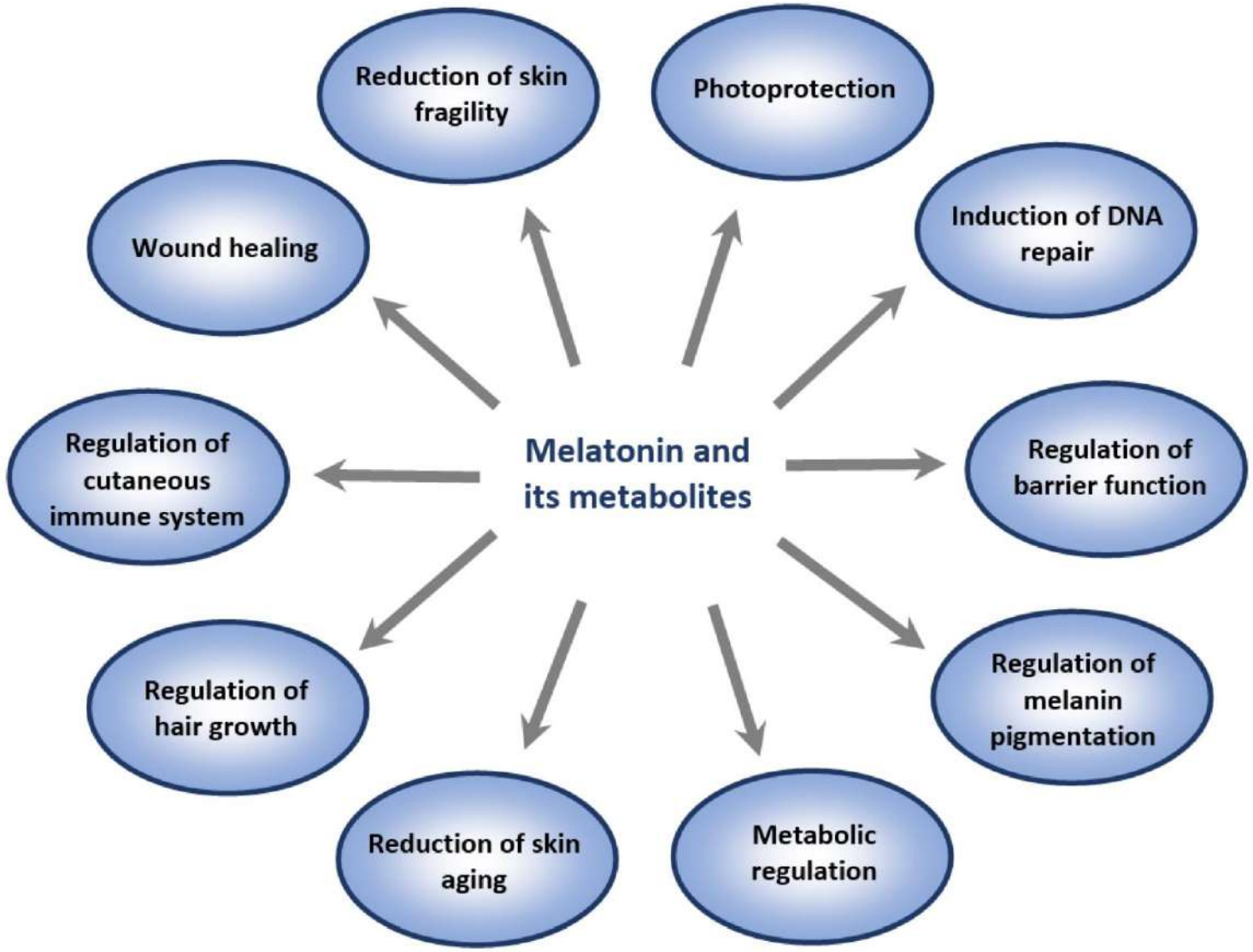
Protective Role of Melatonin and Its Metabolites in Skin Aging



A possible role of melatonin in the prevention and treatment of physiological skin aging. Red crosses (✕) indicate protective action of melatonin against inflammaging, oxidative stress, and mitochondrial damage.

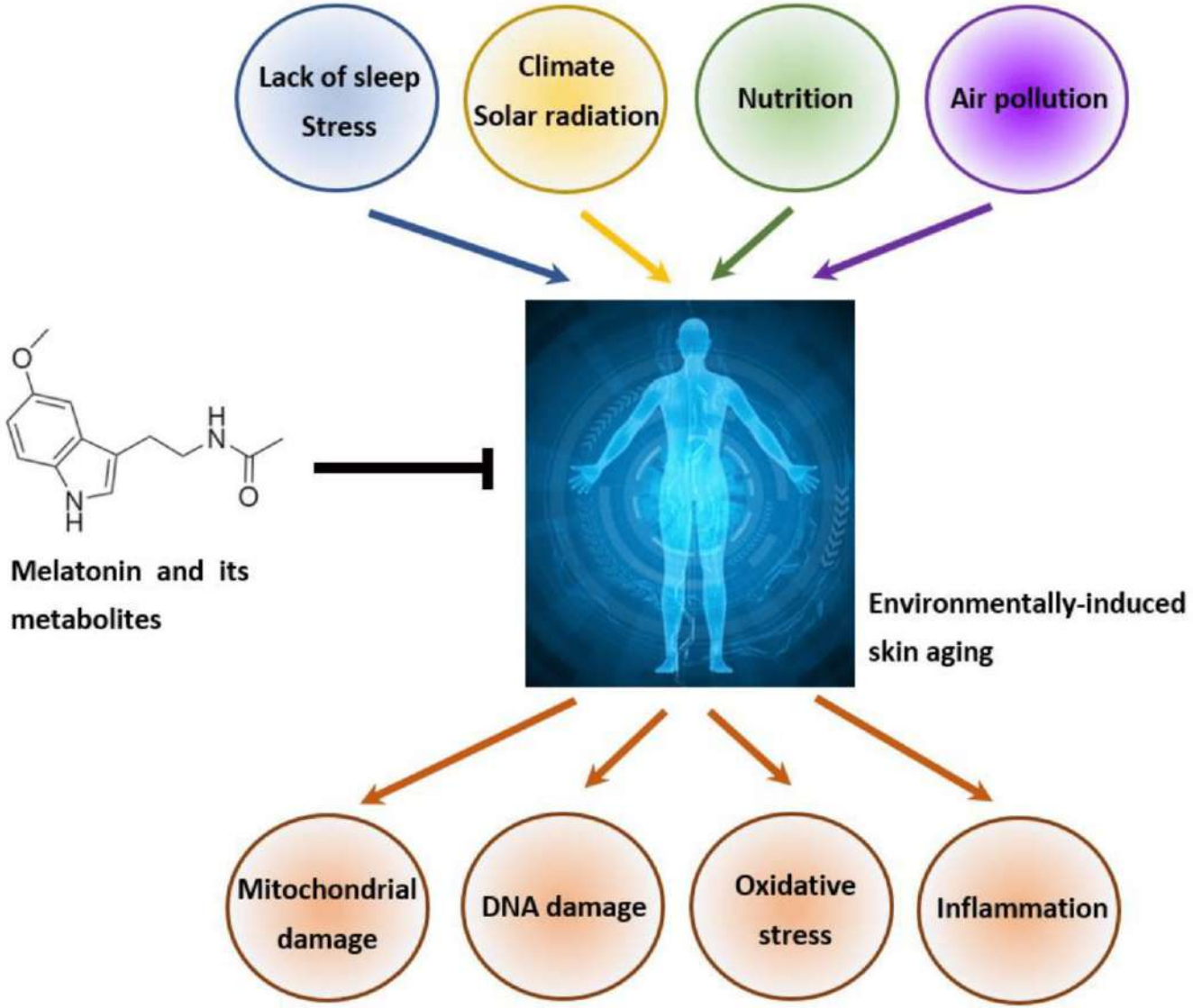
Protective Role of Melatonin and Its Metabolites in Skin Aging. Georgeta Bocheva, Radomir M. Slominski, Andrzej Slominski and All. I*nt. J. Mol. Sci.* **2022**, *23*(3), 1238; https://doi.org/10.3390/ijms23031238

Melatonin and its metabolites are essential for the regulation of many skin functions



Protective Role of Melatonin and Its Metabolites in Skin Aging. **Georgeta Bocheva, Radomir M. Slominski, Andrzej Slominski and All. I***nt. J. Mol. Sci.* **2022**, *23*(3), 1238; **https://doi.org/10.3390/ijms23031238**

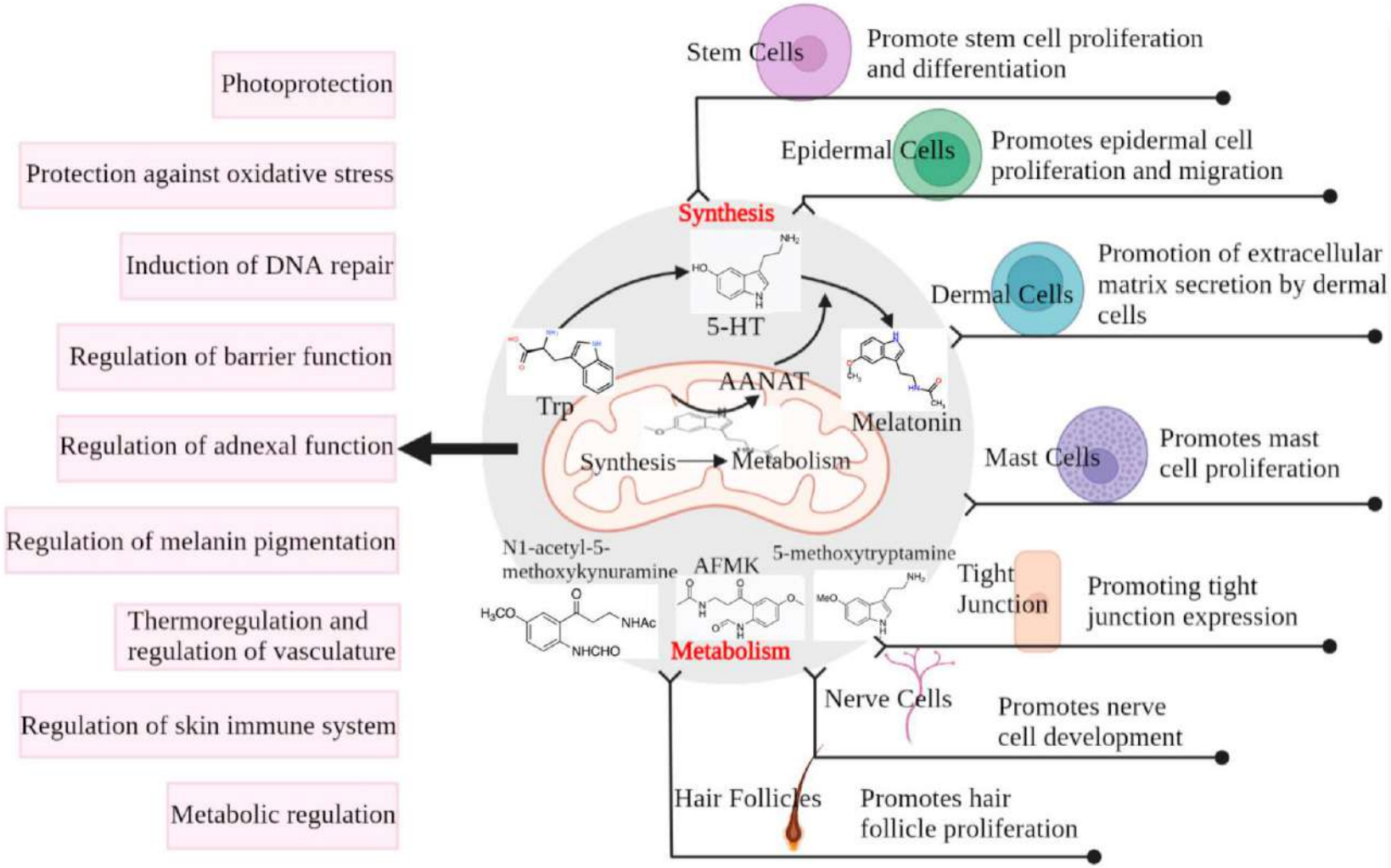
The protective role of melatonin and its metabolites against premature skin aging



Cutaneous melatonin can prevent mitochondrial and DNA damage, oxidative stress, and inflammation caused by environmental factors such as stress, solar radiation, poor nutrition, or air pollution.

Protective Role of Melatonin and Its Metabolites in Skin Aging. Georgeta Bocheva, Radomir M. Slominski, Andrzej Slominski and All. I*nt. J. Mol. Sci.* **2022**, *23*(3), 1238; **https://doi.org/10.3390/ijms23031238**

Melatonin production and metabolism in the skin and its protective effect on the skin.



Cells use AANAT produced in the mitochondria from tryptophan to 5-HT for the eventual synthesis of melatonin, which can also be metabolized in the cells by metabolites such as AFMK. Both melatonin and its metabolites play a regulatory role in different structures of the skin, ultimately protecting the skin from damage

Antioxidants 2023, *12*(5), 1000; https://doi.org/10.3390/antiox12051000

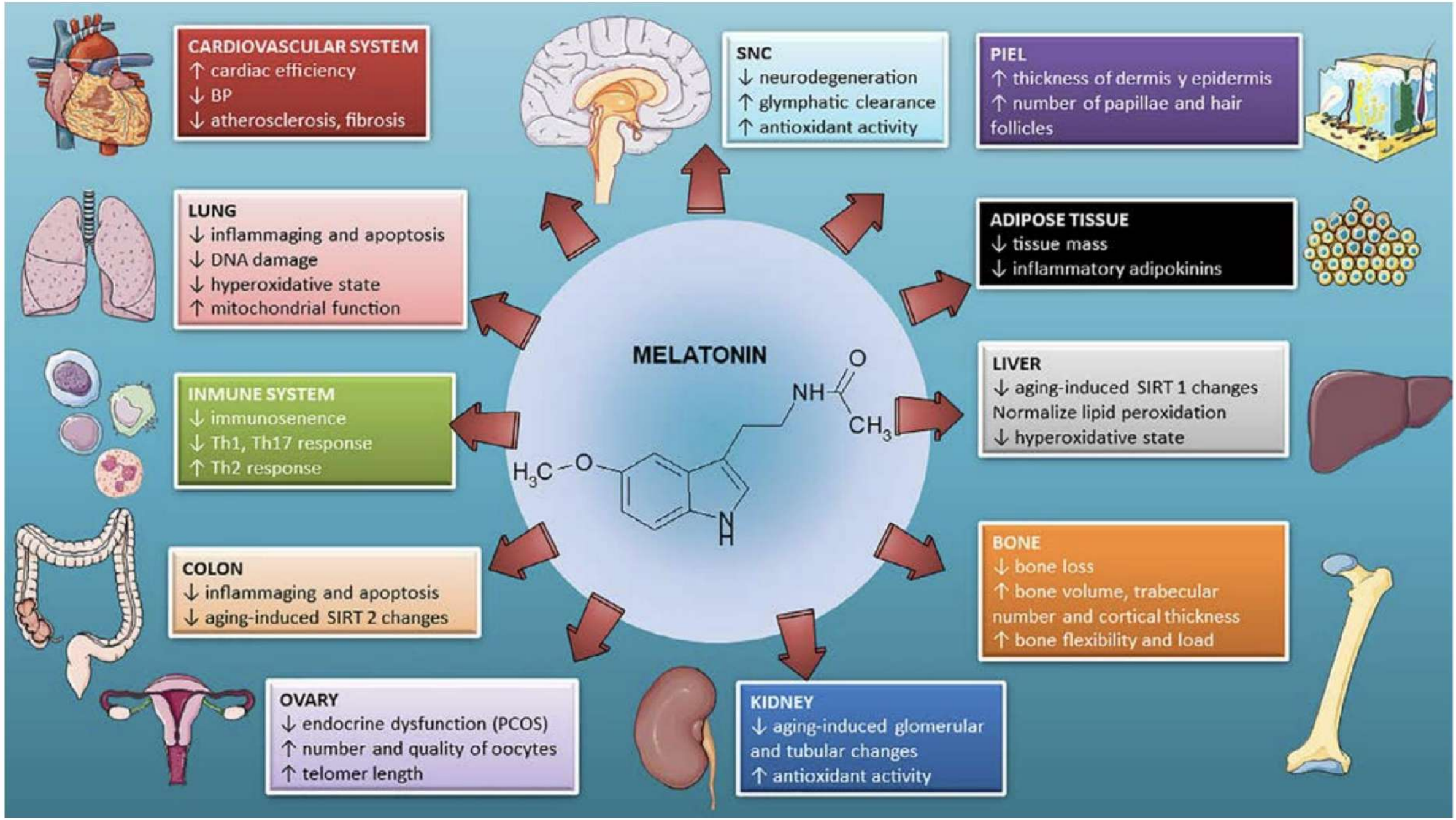
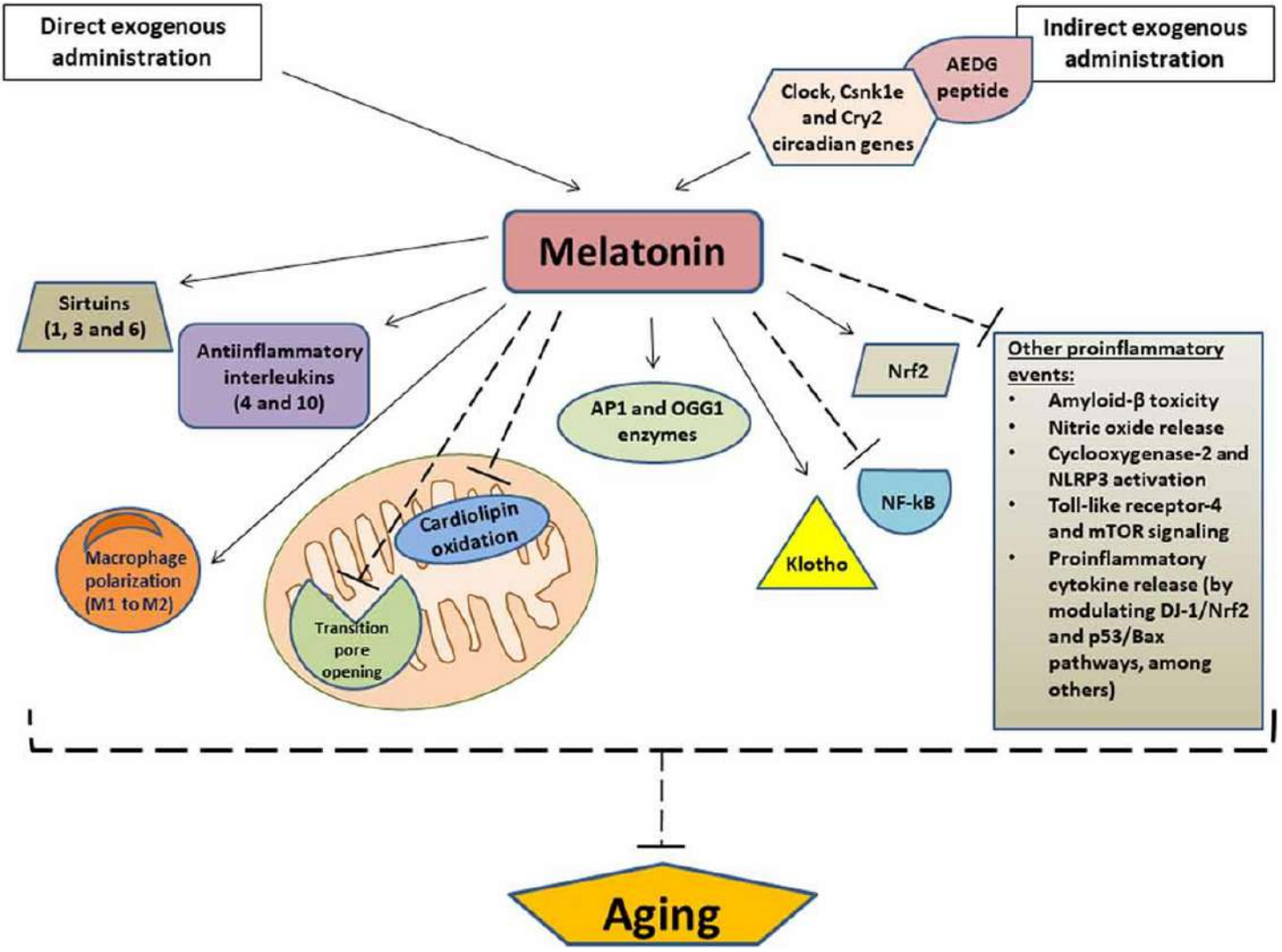


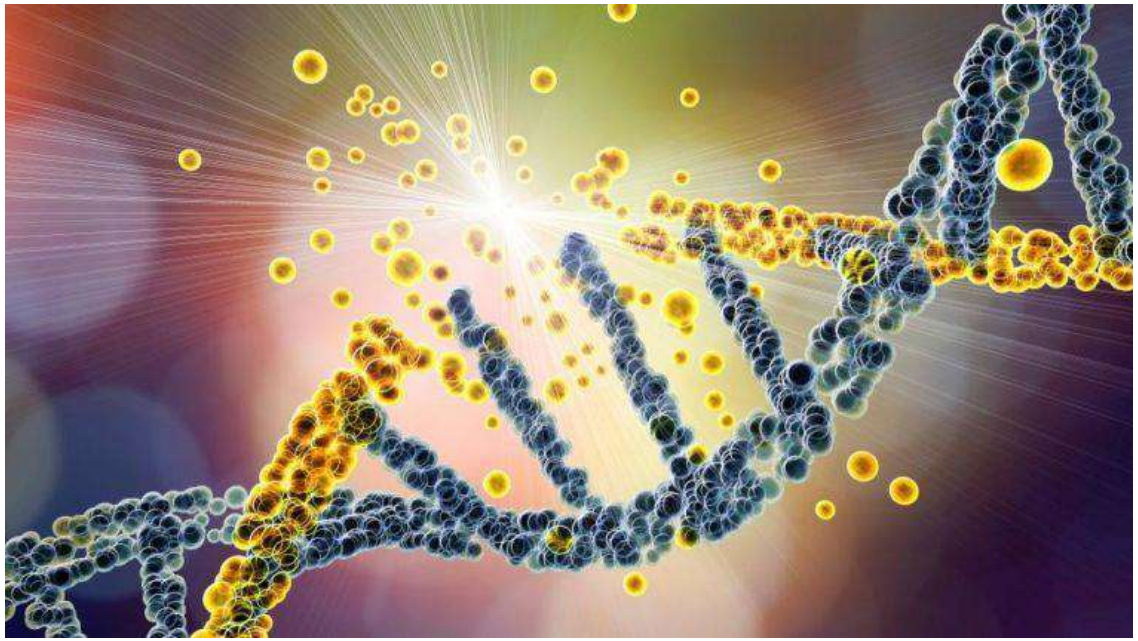
Fig. 2 Melatonin as a cytoprotector in healthy aging. The anti-aging potential of melatonin is shown in different organs.

Melatonin as an Anti-Aging Therapy for Age-Related Cardiovascular and Neurodegenerative Diseases



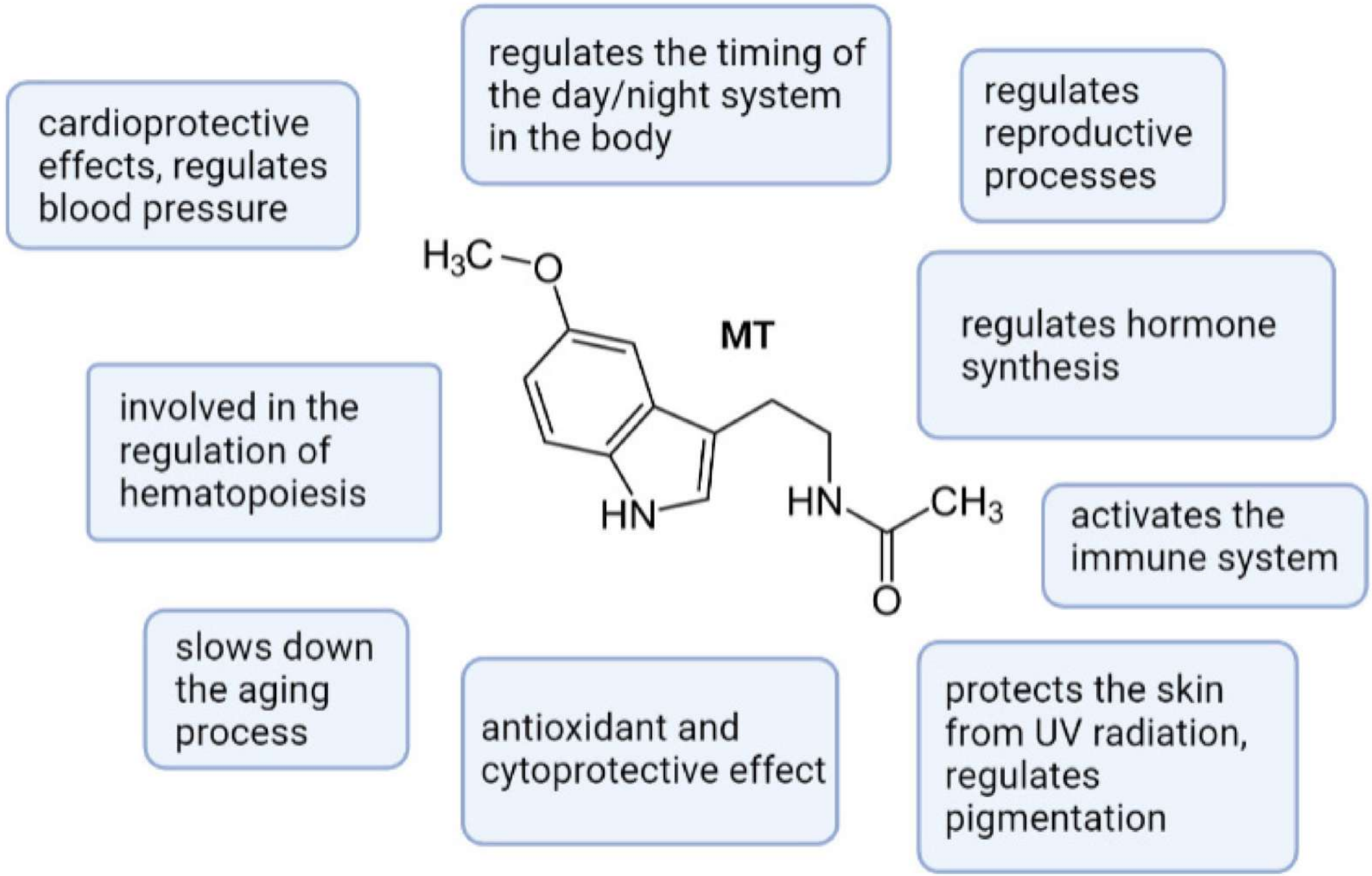
Sirtuin1 (a deacetylase that regulates metabolic activity in response to cellular stress) pathway and the modulation of autophagy, which is decreased during aging. Autophagy is a natural cellular homeostatic mechanism of removing damaged cells, in order to regenerate newer, healthier cells. Therefore, to enhance autophagic processes is crucial to prevent or attenuate cellular aging. In this regard, it was observed that melatonin may increase autophagic activity *via* sirtuin1 in different aging models, which may be therapeutically useful for the prevention and treatment of multiple age-related diseases (Nopparat et al., 2017; Boga et al., 2019). Melatonin also collaborates with sirtuin 3, another NAD^+-dependent deacetylase which, like sirtuin 1, regulates the mitochondrial redox state, among many other functions. Together, melatonin and sirtuin 3 influences mitochondria dynamics and scavenges free radicals, thus preventing or delaying cellular aging and its derived diseases, which are usually developed as a consequence of a redox imbalance (Reiter et al., 2018). In fact, it was observed that the expression patterns of melatonin and different sirtuins (sirtuin 1,3, and 6) significantly decreased in samples of buccal epithelium from old patients compared to young patients, and even more evidently in those who suffer from hypertension. This finding reinforces the likely relationship between age-related diseases (such as hypertension) and melatonin levels (Carbone et al., 2020; Figure 2).

Front. Aging Neurosci., 03 June 2022. Sec. Cellular and Molecular Mechanisms of Brain-aging. Volume 14 - 2022



Melatonin rescue mitochondrial function and repair DNA damages.

Melatonin should be integral part of therapie slowing down aiging process.



Melatonin as the Cornerstone of Neuroimmunoendocrinology. **Igor Kvetnoy, Viktoria Polyakova and All.** *Int. J. Mol. Sci.* **2022**, *23*(3), 1835; **https://doi.org/10.3390/ijms23031835**