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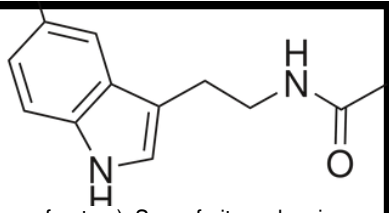
MELATONIN



COMMON NAME: Sleep hormone
SCIENTIFIC NAME: Melatonin or pineal hormone
ACTIVE INGRIDIENTS: N-acetyl-5-methoxytryptamine
OCCURENCE: Plants including Feverfew (Tanacetum parthenium), and St John's wort (Hypericum perforatum). Some fruits and grains like bananas and grapes, rice, wheat, barley, and oats are rich in melatonin. Other foods include herbs, olive oil, coffee, tea, wine and beer.

CLINICAL PROPERTIES

Anti-aging, (8)Antioxidant, (9) (10) Neuroprotective, (11) Anti-inflammatory, (12) Anti-cancer, (13) Antidepressant (14)

CLINICAL SAFETY AND TOXICITY

Melatonin is well tolerated at a dose of 0.3 mg/kg (maximum 20 mg) with no significant adverse events or dose-limiting toxicities.Minor toxicities were weight gain and myelosuppression, which was attributed to the concomitant chemotherapy. (18) Ingestion of 100-mg melatonin by patients before exposure to IR in radiology showed no side effects. (19), (3)

MECHANISM OF ACTION

Melatonin effect on several cancer hallmarks is described below:

(1) Genome Instability and mutation
- Increase in antioxidant enzymes, and DNA repair while decreased pro-oxidative enzymes (21)

(2) Resisting Cell death
- Elevate the expression levels of phosphorylated (p) p38 and p JNK protein, and decrease the expression level of nucleic p p65 (22)
- Inhibit Bcl-2 and upregulate BAD/BAX genes (23)
- Enhance BAX expression, reduce Bcl-xL production, activate caspase-3 and 9, and inhibit the AKT/MDM2 intracellular pathway (24)

(3) Activating Invasion and Metastasis
- Suppression of the ADAMTS family via amplifying of miR-let-7f/miR-181d and reducing protein stability (25)
- Inhibition the NE/AKT/β-catenin/SLUG axis (26)
- Inhibiting of matrix metallopeptidase 13 (MMP-13) (27)
- Inactivation of MMP-2 and MMP-9 signaling pathway (28)

(4) Inducing Angiogenesis
- Inhibiting VEGF expression (29)
- Upregulation of miR-424-5p expression and inhibiting of VEGF (30)
- Inhibition of HIF-1α and STAT3 signaling pathway (31)

(5) Sustained Proliferative Signaling
- Downregulation of PI3K/AKT and NF-κB/iNOS signaling pathways (32)
- Decrease in protein expression of Ki67, , decrease in matrix metalloproteinase 9 (MMP9) (33)
- Significant downregulation of the HIF-1α gene (34,35)
- Reducing expression of cyclin D1, CDK4, cyclin B1, and CDK1 (36)
- Inhibits AP-2β/hTERT, NF-κB/COX-2 and Akt/ERK and activates caspase/Cyto C signaling (37)
- Alteration of MAPK signaling pathway (33)
- Upregulation of p21, p27, and PTEN protein (38)

CLINICAL APPLICATIONS IN ONCOLOGY

1. **Oral uses:**
- Decrease in fatigue levels associated with the malignant condition.(1)
- Significant improvement in markers of objective sleep quality, sleep fragmentation and quantity, subjective sleep, fatigue severity, global quality of life, and social and cognitive functioning scales. (2)
- Melatonin has protective effects against radiation-induced genotoxicity. (3)
- The administration of IL-2 and the pineal hormone MLT may induce control of neoplastic growth and a prolonged survival time in patients with metastatic solid tumors, for whom no other conventional anticancer therapy is available. (4)

2. **Topical uses:** Melatonin oral gel mouthwashes are safe and effective in the prevention and treatment of oral mucositis. (5)
- Significant reduction of radiation dermatitis. (6)
- Topical melatonin administered during radiation therapy could increase the quality of life in patients with primary breast cancer. (7)

SYNERGY WITH CHEMOTHERAPY AND RADIOTHERAPY

- Increases chemotherapy effectiveness. (15)
- Improves disease-related symptoms in heavily pretreated patients with late-stage lung adenocarcinoma and poor performance status. (16)
- Combined treatment of local radiofrequency ablation (RFA) and melatonin (MLT) greatly improved clinical outcomes for early lung cancer patients. (17)

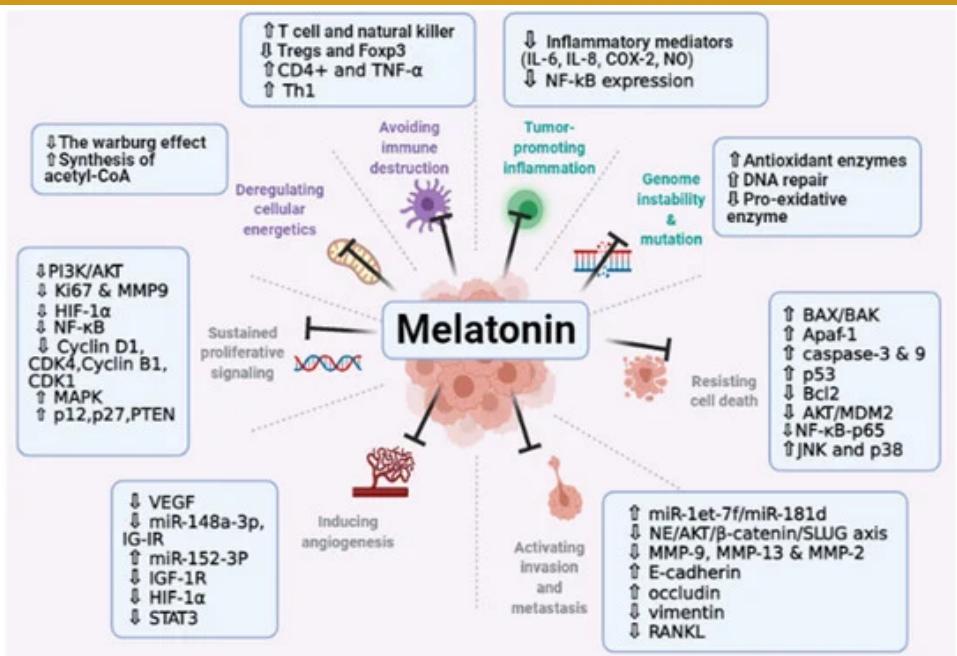


FIGURE A: The effect of Melatonin on multiple targets to exert antitumor effect

(6) Deregulating Cellular energetics
- Inhibition of Warburg effect (39)
- Synthesis of acetyl-CoA from pyruvate by inhibiting the mitochondrial enzyme pyruvate dehydrogenase kinase (PDK) (40)
- Reduce glucose metabolism via downregulation of glycolysis, tricarboxylic acid cycle, and pentose phosphate pathway (41)

(7) Avoiding immune destruction
- Reduced eosinophils, Th17 cells, and Foxp3 expression, as well as increased CD4+ and TNF-α accumulation (42)

(8) Tumor-Promoting Inflammation
- Downregulation of inflammatory mediators (IL-6, IL-8, COX-2, and NO) along with suppression of NF-κB expression (43), (44),(45)

MELATONIN AS AN ANXIOLYTIC

1-Melatonin–Sympathetic Nervous System Interactions:

- Exerts a negative feedback effect on sympathetic system via enhancing GABAergic signaling, which is involved in the inhibition of PVN, RVLM and NTS. (47)
- Enhances nitric oxide (NO) availability, which potentiates the GABAergic inhibitory effects in the PVN and RVLM. (47)

2- Interference of Melatonin with RAAS:

- Attenuates RAAS, reduces Renin and Angiotensin-II to alleviate anxiety symptoms. (48)

3- Melatonin and Glucocorticoids:

- Reduces glucocorticoid receptor density and nuclear translocation through DNMT1 mediated downregulation of FKBP4. (49)

4- Melatonin Interaction with Oxidative and Nitrosative Stress:

- Elevates glutathione, superoxide dismutase and glutathione peroxidase and reduces malondialdehyde. (50)

5-Melatonin-Induced Modifications of Neurotransmission:

- Reduces Dopamine to reduce anxiety. (51)

MELATONIN INDUCED SEDATION

- Melatonin binds to transmembrane receptors MT1 and MT2 present in SCN, recruits β-arrestin, activates G proteins and inhibits adenylyl cyclase activity. (52), (53)
- MT1 coupling to G proteins activates phospholipase C (PLC), which leads to activation of IP3 and DAG. Activation of IP3 causes an increase in intracellular Ca2+ and activated DAG increases PKC. (52),(54)
- MT2 receptor mediated G proteins activation reduces cAMP, PKA and resultantly CREB expression level also declines in nucleus. cAMP when decreased, induces transition from wakefulness to sleep. (55)
- Increased PKC and reduced PKA act on GABA A receptor and induce receptor phosphorylation thus making it more responsive to GABA. This makes a reduction in neuronal excitation. Also the miniature inhibitory postsynaptic current (mIPSC) and Cl ion influx increase to potentiate sedative effect. (56)

ANTIDEPRESSANT MECHANISM

1-Inhibition of neuroinflammation:

- (inhibits JNK, NF-κB, endoplasmic reticulum stress(57), overactive astrocytes and microglia and production of proinflammatory cytokines (TNF-α and IL-1β) to reverse depression). (58)

2-**Inhibition of oxidative stress:**

- (reverse the altered redox signaling molecules like AKT and Nrf2 (59), inhibit ROS and Lipid Peroxidase (LPO), and increases catalase (CAT) and Super Oxide Dismutase (SOD). (60)

3-**Autophagy:**

- normalize autophagy-related gene expression (Beclin-1, p62, Atg5 and Atg4, through FOXO3a signaling). (59)

4-**Upregulation of neurotransmitters** :

- Upregulates Serotonin(5-HT) and Nor Epinephrine. (61)

5-**Upregulation of neurotrophic factors:**

- Upregulates neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF). (62)

6-**Promotion of neuroplasticity:**

- Blockage of NMDA receptor strengthens melatonin anti-depressant effects. (63)

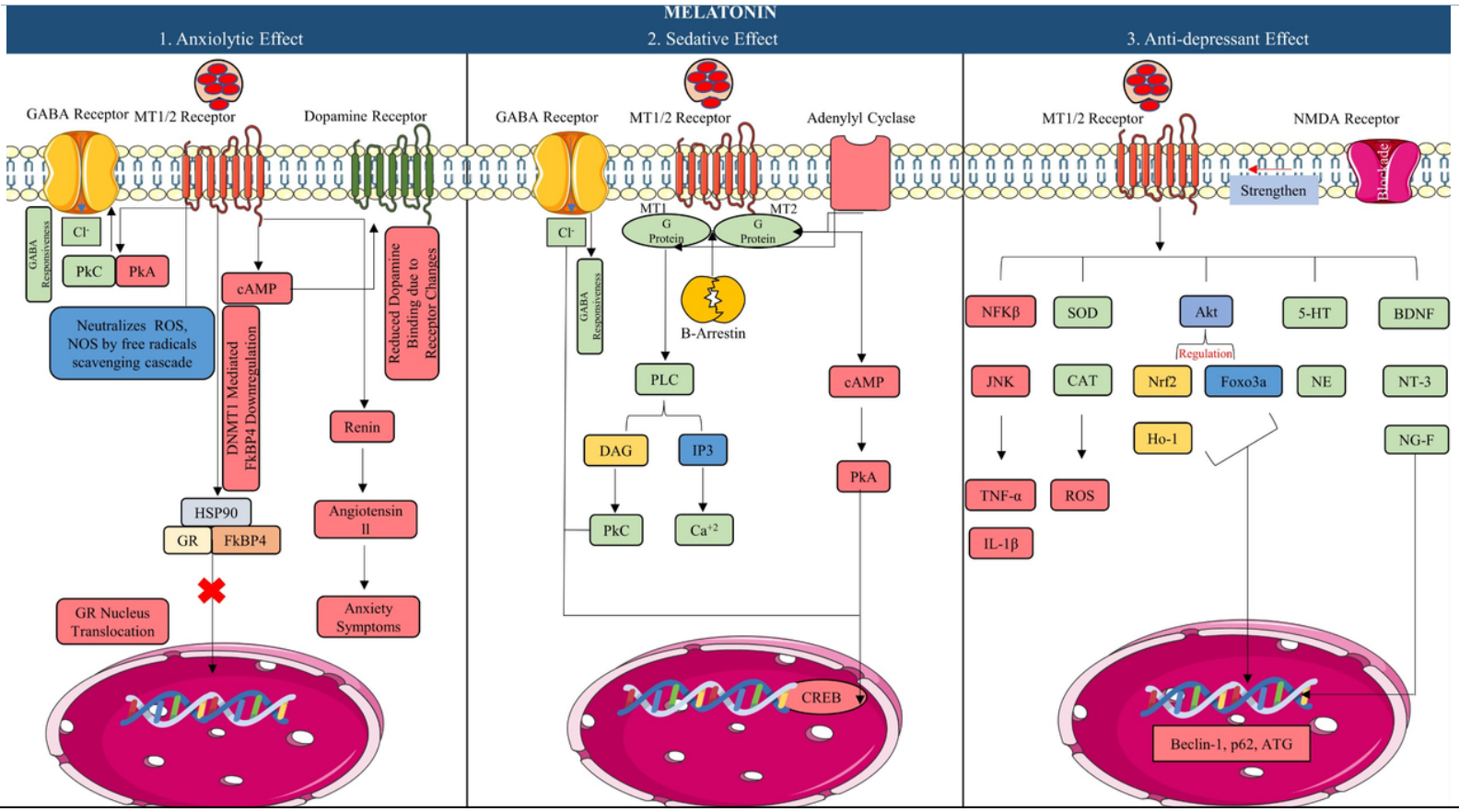


Figure B. Molecular targets of Melatonin to exert anxiolytic, sedative and anti-depressive effects

DOSE RECOMMENDED IN PUBLISHED CLINICAL TRAILS OF CANCER

- Sedation: 6 mg oral melatonin approximately 1 hour before bedtime resulted in significantly increased sleep efficiency (46)
- Supportive care: MLT 20 mg/day (4)
- Radioprotection: ingestion of 100-mg melatonin by patients before exposure to IR in radiology (19)

"PUROBEST MELATONIN" RECOMMENDED DOSAGE

One to two capsules of Purobest Melatonin once a day or as directed by the healthcare practitioner.

Formulation Characteristics: Each Purobest Melatonin capsule contains 10mg of melatonin. Quality of active ingredient is ensured via third party testing.

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