Melatonin as a Food Supplement and Drug: Routes of Administration and Formulations

Nikol-Anna Voulgari
The American College of Greece, Deree

RESEARCH QUESTIONS

The research questions that were addressed in the Capstone paper are:

A) Which is the least effective form and route of administration of melatonin, and what are the reasons?
B) Which other forms and routes of administration are available for melatonin, that are more effective?
C) Are botanical blends better formulations than melatonin in its pure form?
D) Are all ingredients in melatonin botanical blends a safe option for all patients?

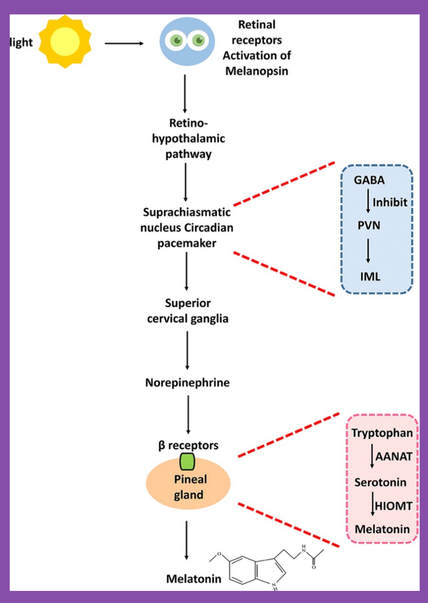


Figure (1): Mechanism of production of melatonin in the pineal glands.

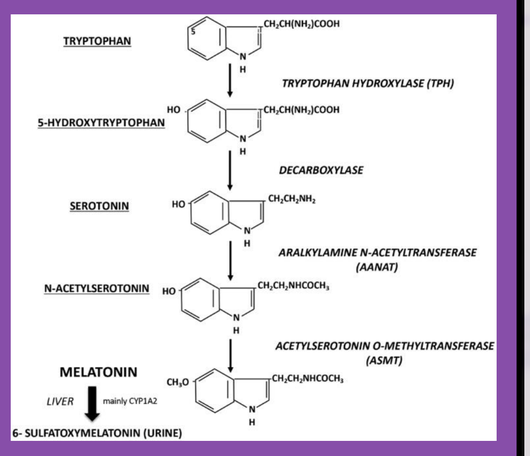


Figure (2): The pathway of synthesis of melatonin and hepatic metabolization.

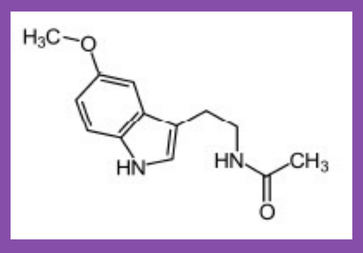


Figure (3): Melatonin chemical structure (N-acetyl-5-methoxytryptamine).

CONTACT INFORMATION

Nikol-Anna Voulgari
The American College of Greece, Deree
Email: N.Voulgari@acg.edu

INTRODUCTION

Melatonin is a hormone that is produced naturally in the body in response to darkness and can be found in all organisms including vertebrates, invertebrates, plants, bacteria, unicellular eukaryotes and macroalgae. In mammals, melatonin, is mostly produced as a hormone in the pineal gland, a small (100-150 mg), pinecone shaped, unpaired, highly vascularized, secretory, epithalamic neuroendocrine gland, found in the mid-line (center) of the brain. However, it can be produced by several cells, such as lymphocytes, tissues such as the retina and organ systems, such as the skin. Moreover, melatonin is secreted by the pinealocytes, and more specifically α- and β-pinealocytes.

The mechanism of production of melatonin in the pineal glands is also summarized in Figure (1). The synthesis of melatonin starts from tryptophan and includes four steps and involves four enzymes, as seen in Figure (2). Melatonin's chemical structure is depicted in Figure (3).

The Capstone Project focuses on the the routes of administration of melatonin such as the oral, sublingual, nasal, transdermal and intravenous and explains why the oral one is less effective in terms of bioavailability. Lastly, it explores melatonin formulations with melatonin as a sole ingredient or combined with other ingredients in terms of safeness and positive and negative effects.

METHODOLOGY

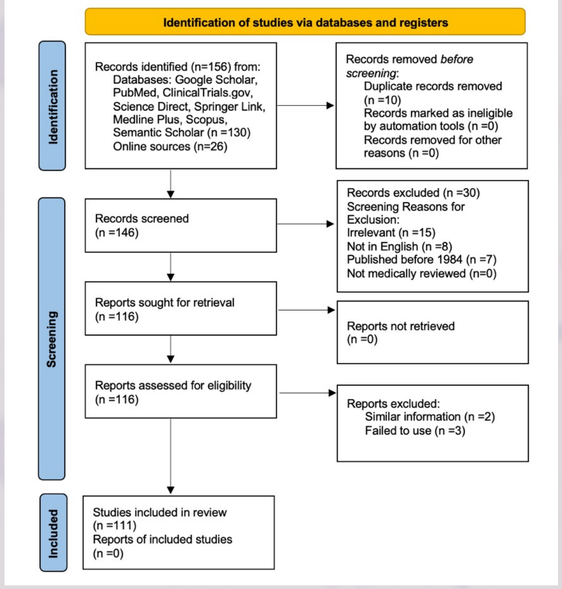


Figure (4): PRISMA 2020 flow diagram of systematic Capstone literature review paper.

THEMATIC DISCUSSION

There are different routes of administration of melatonin which have different outcomes in terms of availability:

A) Oral: through pills/tablets, liquid syrups and gel gummies.
- **Tablets:** immediate-release (IR), extended-release (ER) or delayed-release (DR).
- **Tablets:** without coating, with a film coat or chemical envelope, soft-gel capsules, hard-shell capsules, effervescent (fizzy) tablets.
- **Liquid syrups/drops:** easy administration for those that cannot swallow.
- **Gel gummies:** when chewed, part of the melatonin is absorbed through the oral mucosa and bypasses the liver and consequently the first-pass effect.
- Around 85-90% of the melatonin ingested undergoes the hepatic first-pass metabolism, decreasing the absorption rates and bioavailability.
- First-pass metabolism of melatonin→ gastric lumen→ gut wall→ small intestinal lumen→ intestinal walls of the small intestine→ portal vein of the portal circulation→ liver→ systemic circulation
- Liver cytochrome P450s (CYP450), CYP1A2, CYP2C19, CYP1A1, play an important role in the hepatic metabolism of melatonin.
- CYP1B1, located in the intestine and the cerebral cortex, plays a role in the metabolism of melatonin.
- The bioavailability of this route is 15% (Figure (5)).

B) Buccal and Sublingual: **through patches (for buccal), film/strips, spray, and granules.**
- **Patches and films:** when dissolved, melatonin is absorbed by the lining of the mouth into the systemic venous circulation and spreads throughout the whole body and system via the bloodstream.
- **Spray:** melatonin is absorbed by the high vascularization under the tongue.
- **Granules:** melatonin is absorbed through the lining of the mouth.
- Through the veins of the systemic circulation, melatonin bypasses the hepatic portal circulation and avoids the hepatic first-pass metabolism.
- Part of a dose may be swallowed and will undergo the first-pass effect.
- The bioavailability of this route is 70% (Figure (5)).

C) Intranasal: **through inhalation of a nasal spray.**
- Melatonin moves across the nasal mucosa, gets absorbed by the vascular system of the nasal mucosa and is released to the general circulation.
- Avoids the biotransformation organs of the first-pass metabolism.
- The bioavailability of this route is 74.5% (Figure (5)).

D) Transdermal: **through transdermal patches.**
- **Patches:** porous and non-rate-limiting membranes with an active contact area.
- Extended/prolonged duration due to the thickness of the skin.
- Melatonin undergoes the first-pass metabolism, in a small degree, in the skin, blood, and vascular endothelium.
- Bypasses the hepatic first-pass effect.
- The bioavailability of this route is 45% (Figure (5)).

E) Intravenous: **through the veins, via IV bolus or IV infusion.**
- Directly in the systemic circulation with rapid onset of action.
- Melatonin avoids the first-pass effect and the defects that it may cause to the drug/health supplement.
- The bioavailability of this route is 100% (Figure (5)).

As it is indicated in Figure (5), the aforementioned routes of administration of melatonin are not bioequivalent and the least effective one is the oral, since the bioavailability can be decreased from the extensive first-pass metabolism that the molecule undergoes.

Melatonin supplements are found in various formulations, where the active ingredient is in its pure form, or it is combined with other substances, as a botanical blend, to enhance and optimize its action and add other effects or therapeutic benefits. This paper analyzes the benefits and side effects of popular ingredients that are added to melatonin supplements such as cannabidiol, ashwagandha, valerian, magnesium, and tryptophan, and whether they are a safe option for different categories of patients (Table (1)).

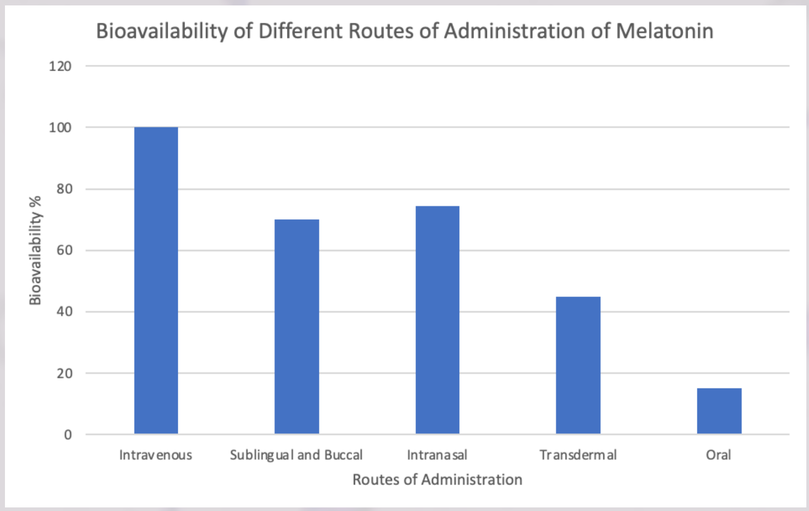


Figure (5): Differences in the bioavailability of routes of administration of melatonin mentioned in the Capstone Paper.

CONCLUSION

- The least effective route of administration is the oral due to decreased melatonin bioavailability from the first-pass hepatic metabolism.
- More effective routes of administartion than the oral are, the sublingual, nasal, transdermal, and intravenous.
- Melatonin botanical blends are better forms of supplements due to the properties of ingredients.
- Melatonin botanical blends are not safe options for all patients due to, side effects of ingredients, drug-drug interactions and because there are inconclusive studies.

Table (1): Benefits and side effects of popular ingredients contained in melatonin botanical blends

Ingredients	Benefits	Side Effects	Patients that should avoid the ingredients
Melatonin	Analgesic, antioxidant, anti-inflammatory, antidepressant, anti-tumor, anxiolytic, regulates the sleep-wake cycle Treatment for: endocrine, metabolic, neurogenerative and GI disorders, pain syndromes, cardiovascular diseases	Sleepiness, drowsiness, fatigue, headache, agitation, hypertension, anxiety, dysphoria, swelling, rashes, flushing, hormone imbalance, irritability, mood swings	Those that consume: Immunosuppressants, antidepressants, antidiabetics, oral contraceptives, antibiotics, nonsteroidal anti-inflammatory agents, antidiabetics, blood pressure medications, anticoagulants, cimetidine, benzodiazepines, zolpidem Pregnant or breastfeeding women
Cannabidiol (CBD)	Antidepressant, anti-epileptic, anxiolytic, analgesic, antioxidant, anticonvulsant, anti-inflammatory, antipsychotic, promotes sleep	Sedation, euphoria, sleepiness, tiredness, vomiting, fatigue, diarrhea, hepatic issues, dry mouth, disorientation, drowsiness, paranoia, psychosis, neurotoxicity, addiction	Those that consume: Melatonin, benzodiazepines, antiepileptic drugs, antidepressants, opioids
Ashwagandha	Sedative, anxiolytic, analgesic, antioxidant, diuretic, hypotensive, hematopoietic, immunomodulatory, memory improvement Treatment for: Insomnia, senile dementia, asthma, bronchitis, gastric ulcers	Sedation, hypnosis, headache, diarrhea, drowsiness, nausea, vomiting, GI issues, hepatotoxicity, jaundice, infertility, pregnancy issues	Those that consume: Antidiabetics, benzodiazepines, immunosuppressants, CNS depressants, antihypertensives, thyroid hormone medications Those with hormone-sensitive cancers Those with hyperthyroidism Pregnant women
Valerian	Anxiolytic, mood stabilization, antidepressant, improves sleeping time, menopausal symptoms, menstrual cramps, premenstrual syndrome symptoms	Pruritus, dizziness, drowsiness, headache, GI issues, excitability, vivid dreams, insomnia, uneasiness, dry mouth, GI issues, heart disturbances, mental dullness, sedation, insomnia	Those that consume: Medications broken down by the liver, benzodiazepines, barbiturates, tricyclic antidepressants, opioids, kava, statins, antihistamines, St. John's wort, melatonin Pregnant or breastfeeding women Children under the age of 3
Magnesium	Anxiolytic, antidepressant, improves sleep quality Treatment for: migraines, stroke, asthma, coronary artery disease, myocardial infarction, preeclampsia	Diarrhea, GI issues, vomiting, nausea, abdominal cramping, mineral deficiency, facial flushing, urine retention, lethargy, hypotension, hypertension, coma, cardiac arrhythmias, cardiac arrest, respiratory paralysis, depression	Those that consume: Antibiotics, diuretics, bisphosphonates, proton pump inhibitors, blood pressure medications, antidiabetics, aminoglycosides, digoxin, melatonin
Tryptophan	Analgesic, anxiolytic, antidepressant, improves cognitive function, social function, premenstrual dysphoric disorder symptoms, chronic fatigue, Treatment for: Attention deficit/hyperactivity disorder, autism, inflammatory bowel disease, cardiovascular diseases, multiple sclerosis, chronic kidney disease, eating disorders, microbial infections, sleep disorders	Diarrhea, vomiting, nausea, headache, stomach pain, tremor, drowsiness, blurry vision	Those that consume: CNS depressants, antidepressants, St. John's wort, 5-HTP, black seed, SAMe, valerian, kava, hops, melatonin Pregnant or breastfeeding women

© Poster Template by Genigraphics® 1.800.790.4001 www.genigraphics.com