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EFFECTS OF MELATONIN IN DISEASES OF THE DIGESTIVE SYSTEM. LITERATURE REVIEW

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Abstract

Introduction: Melatonin is involved in many biological and physiological processes in the body. In recent years, its protective effect on the digestive system has been investigated in many ways and the therapeutic role of melatonin in gastrointestinal pathologies has been investigated.

Aim: review of the literature on the clinical effects of melatonin in digestive system diseases, characteristics of its place in clinical use.

Search strategy: "The effect of melatonin in diseases of the digestive system" in 3 languages (Russian, Turkish and English), sampling depth 10 years, Web of Science, PubMed, Google Scholar, Dergipark entry data were used. As a result, 806 articles were found, of which 53 articles were selected. *Inclusion criteria:* full versions of articles of randomized and cohort studies, reports, dissertations, protocols. *Exclusion criteria:* abstracts, articles, scientific publications describing a single case, summaries of reports.

Results and conclusions. Taken together, the studies revealed that melatonin is an effective chronobiological molecule that can act in different directions. In this regard, it is not surprising that it is widely used in clinical practice, especially in terms of its mucosal protective effects. As a result of clinical studies, positive results have been achieved in the protective effect of melatonin in gastric and intestinal ulcer diseases, in the reduction of complaints of patients in gastroesophageal reflux diseases. As a result of several studies, a positive significance has been recognized in the protection against damage caused by aggressive factors that lead to the disruption of the digestive system. In addition, it has many positive effects in liver pathologies of the digestive system (non-alcoholic fatty liver disease, hepatosteatosis), intestinal diseases (Crohn's disease, its inflammatory frequency and ulcerative colitis, and in prolonging the remission stage), especially in irritable bowel syndrome. conclusions cannot be ignored.

Different lines of research continue to elucidate the role, function, and potential pharmacological effects of melatonin in the gastrointestinal system, and the topic remains relevant.

Keywords: *Melatonin, biological clock, antioxidant, gastrointestinal system.*

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Резюме

ЭФФЕКТЫ МЕЛАТОНИНА ПРИ ЗАБОЛЕВАНИЯХ ОРГАНОВ ПИЩЕВАРЕНИЯ. ОБЗОР ЛИТЕРАТУРЫ

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Актуальность. Мелатонин участвует во многих биологических и физиологических процессах в организме. В последние годы широко изучается его защитное действие на пищеварительную систему и исследуется терапевтическая роль мелатонина при патологиях желудочно-кишечного тракта.

Цель исследования: обзор литературы о клинических эффектах мелатонина при заболеваниях органов пищеварения, характеристика его места в клиническом применении.

Стратегия поиска: «Действие мелатонина при заболеваниях органов пищеварения» на 3-х языках (русском, турецком и английском), глубина выборки 10 лет, использованы входные данные Web of Science, PubMed, Google Scholar, Dergipark. В результате было найдено 806 статей, из них отобрано 53 статьи. *Критерии включения:* полные версии статьи рандомизированных и когортных исследований, отчеты, диссертации, протоколы. *Критерии исключения:* авторефераты, статьи, научные публикации описывающие единичные случай, резюме докладов.

Результаты и выводы. В совокупности исследования показали, что мелатонин является эффективной хронобиологической молекулой, которая может действовать в разных направлениях. В связи с этим неудивительно, что он широко используется в клинической практике, особенно с точки зрения его защитного действия на слизистую оболочку. В результате клинических исследований достигнуты положительные результаты по защитному действию мелатонина при язвенной болезни желудка и кишечника, уменьшению жалоб больных гастроэзофагеальной рефлюксной болезнью. В результате ряда исследований признано положительное значение защиты от повреждений, вызванных агрессивными факторами, приводящими к нарушению работы пищеварительной системы. Кроме того, нельзя игнорировать множество положительных эффектов при печеночных патологиях органов пищеварения (неалкогольная жировая болезнь печени, гепатостеатоз), заболеваниях кишечника (болезнь Крона, частота ее воспалительного процесса и язвенный колит, при удлинении стадии ремиссии), особенно при раздраженном кишечнике.

Различные направления исследований продолжают выяснять роль, функцию и потенциальные фармакологические эффекты мелатонина в желудочно-кишечной системе, и эта тема остается актуальной.

Ключевые слова: *Мелатонин, биологические ритмы организма, антиоксидант, желудочно-кишечная система.*

Для цитирования:

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Түйіндеме

МЕЛАТОНИННІҢ АСҚОРЫТУ ЖҮЙЕСІ АУРУЛАРЫНДА ӘСЕРІ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Мелатонин организмде көптеген биологиялық және физиологиялық процестерге қатысады. Соңғы жылдары асқорыту жүйесіне қорғаушы әсері көптеген бағыттарда зерттелуде, асқазан-ішек жолы патологияларындағы мелатониннің емдік рөлін зерттеу болып табылады.

Зерттеудің мақсаты: Мелатониннің асқорыту жүйесі ауруларында әсерін клиникасын, клиникалық қолданудағы орнының ерекшеліктерін бойынша әдебиеттерге шолу.

Іздеу стратегиясы: Web of Science, PubMed, Google scholar, Dergipark кіріс деректерін пайдалана отырып, 3 тілде «Мелатониннің асқорыту жүйесі ауруларында әсері» (орыс, түрік және ағылшын), таңдау тереңдігі 10 жыл. Нәтижесінде 806 мақала табылды, одан 53 мақала таңдалды. *Қосу критерийлері:* рандомизацияланған және когорттық зерттеулердің толық нұсқалары, есептер, диссертациялар, хаттамалар. *Ерекшелік критерийлері:* авторефераттар, мақалалар, бір жағдайды сипаттайтын ғылыми жарияланымдар, баяндамалардың қысқаша мазмұны.

Нәтижелер мен қорытындылар. Зерттеулерді тұтастай алғанда, мелатониннің әртүрлі бағыттарда әрекет ете алатын тиімді хронобиологиялық молекула екендігі анықталған. Осыған байланысты, клиникалық тәжірибеде, әсіресе оның шырышты қабатты қорғайтын әсерлері тұрғысынан клиникада кеңінен қолданылуы таңқаларлық емес. Асқазан–ішек жара ауруларында мелатониннің протективті әсері, гастроэзофагеальді рефлюкс ауруларында науқастардың шағымының азаюында клиникалық зерттеулер нәтижесінде оң нәтижелерге қол жеткізілген. Асқорыту жүйесінің бұзылысына алып келетін агрессивті факторлардың салдарынан зақымданудан қорғауда бірнеше зерттеулер нәтижесінде оң мәнділік танылған. Сонымен қатар, асқорыту жүйесінің бауыр патологияларында да (алкогольді емес бауырдың май басу ауруы, гепатостеатоз) ішек ауруларында (Крон ауруы, оның қабыну жиілігі мен ішектердің ойық жара колиттерінде ремиссия сатысын ұзартуда жоғары нәтижелерге қол жеткізілген), әсіресе тітіркенген ішек синдромында оның көптеген оң әсерлері туралы қорытындыларды елемеуге болмайды.

Әр түрлі бағыттағы зерттеулер мелатониннің асқазан-ішек жүйесіндегі рөлін, қызметін және ықтимал фармакологиялық әсерін анықтауды жалғастыруда және тақырып әлі де өзекті болып қала береді.

Түйінді сөздер: *Мелатонин, биологиялық ритм, антиоксидант, асқорыту жүйесі.*

Дәйексөз үшін:

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Introduction

Melatonin participates in numerous biological and physiological processes in the body. It has many important functions, including cell regeneration, strengthening the immune system, regulating sleep patterns, and controlling body temperature. This indole is one of the strongest antioxidants due to its lipophilic properties. As a result of these properties, it easily disseminates throughout the body and can cross the blood-brain barrier.

Melatonin and its agonists, which are used to treat sleep disorders, as well as their role as antidepressants, are still being studied in the treatment of many diseases. Until recently, however, melatonin itself and its agonists have been used clinically only for conditions such as jet lag syndrome, insomnia, and depression associated with sleep disturbances. Meanwhile, new findings regarding the unique characteristics of melatonin produced in the gastrointestinal tract are emerging, highlighting its therapeutic potential in various pathological conditions, and research in this area is ongoing. This literature review explores the role of melatonin in the physiology and pathologies of the gastrointestinal tract (GIT) based on recently published studies.

Melatonin is a natural neurotransmitter that plays a role in regulating numerous biological and physiological processes in the body, including sleep and biological rhythms (circadian rhythms). Its primary function is to control the body's biological clock and maintain rhythmicity [1]. Melatonin (chemically known as 5-methoxy-N-acetyltryptamine) is an indole hormone that is mainly secreted by the pineal gland. In addition to the brain, it is also synthesized in other peripheral tissues and systems, such as the bone marrow, platelets, lymphocytes, and the skin, thereby influencing multiple physiological systems [2–6].

Its effects on cell regeneration and the immune system, as well as its other well-known functions, have been widely recognized. This literature review focuses on the general characteristics of the hormone melatonin and discusses the role of melatonin synthesized in the gastrointestinal tract (GIT) for the body, along with its effects on physiological and pathological processes. Melatonin is synthesized in the gastrointestinal tract by enterochromaffin cells, and the intensity of this synthesis is coordinated with the rhythm of food intake. The concentration of melatonin in the GIT is approximately 10–100 times higher than its concentration in the blood. In fact, the total amount of melatonin present in the gastrointestinal mucosa is about 400 times greater than that found in the pineal gland [4–5].

Objective: To analyze the effects of melatonin in diseases of the digestive system and to evaluate the specific features of its role in clinical practice based on current evidence.

Search strategy: To meet international standards, this review followed the systematic review reporting criteria outlined by PRISMA for reviews and meta-analyses. Systematic searches were conducted using the following databases: Web of Science, PubMed, Google Scholar, and Dergipark. The search was performed in three languages (Russian, Turkish, and English) using the keywords "Effects of melatonin in diseases of the digestive system", with a publication time frame of the last 10 years. As a result, 806 articles were identified, of which 53 were selected for inclusion**.**

*Inclusion Criteria***:** Full-text randomized controlled trials and cohort studies, reports, dissertations, and study protocols**.**

Exclusion Criteria: Abstracts only, review articles, single-case reports, and conference abstracts.

Results

Synthesis of the hormone melatonin

Tryptophan, the precursor of melatonin synthesis, is an essential amino acid that is obtained from the diet. After being taken up from the plasma by the pineal gland, tryptophan undergoes hydroxylation by the enzyme tryptophan hydroxylase. In pinealocytes, this reaction leads to the formation of 5-hydroxytryptophan, the first intermediate in melatonin synthesis, which can readily cross the blood–brain barrier. Using tetrahydrobiopterin (BH_4) and superoxide (O_2) as cofactors, along with vitamin B_6 as a coenzyme, 5-hydroxytryptophan is then converted into 5-hydroxytryptamine (serotonin) by the enzyme 5-hydroxytryptophan decarboxylase. Serotonin itself cannot cross the blood–brain barrier. Subsequently, serotonin is acetylated by the enzyme N-acetyltransferase (NAT) to form N-acetylserotonin. Finally, N-acetylserotonin is methylated by hydroxyindole-O-methyltransferase (HIOMT) to produce N-acetyl-5-methoxytryptamine, i.e., melatonin [7–9].

Sites of melatonin synthesis

In mammals, melatonin is secreted by the pineal gland, bile and gastrointestinal tract, and the retina. In the retina, melatonin produced by the retinal pigment epithelium and photoreceptors plays a role in regulating retinal responses to day–night changes. Melatonin synthesized in the skin contributes to tissue adaptation and protects against harmful solar radiation. After food intake, melatonin produced by enterochromaffin cells in the gastrointestinal tract is released into the bloodstream. Melatonin synthesized in the bile protects the mucosa and epithelium of the bile ducts from oxidative damage caused by oxidized cholesterol derivatives and bile acids. However, the contribution of this peripheral synthesis to circulating melatonin levels is very small. Approximately 80% of melatonin in the bloodstream is synthesized by the pineal gland [7,10].

Melatonin receptors

Three types of melatonin receptors have been identified. Activation of the MT1 receptor exerts its effect by reducing adenylate cyclase activity in cells. This receptor is involved in regulating the retina, kidney function, biological rhythms, reproductive functions, and constriction of cerebral arteries [11]. In contrast, MT2 and MT3 receptors act via phosphoinositide hydrolysis. Melatonin receptors are present in various regions of the human brain, the intestine, ovaries, and blood vessels. Notable agonists include melatonin analogs such as Ramelteon, Tasimelteon, and Agomelatine, which are used in the treatment of sleep disorders and depression [11,12].

Pharmacokinetics

In the blood, 60–70% of melatonin is bound to albumin. The half-life of melatonin ranges from 3 to 45 minutes. Due to its partial solubility in both water and lipids, melatonin easily penetrates tissues and cells. Melatonin is primarily metabolized in the liver to 6-hydroxymelatonin, which is then converted through a series of reactions to N-acetyl-5-methoxy-6-hydroxytryptamine. It is subsequently conjugated with sulfate or glucuronide to form 6-sulfatoxymelatonin, which is excreted in the urine. Less than 1% of melatonin is excreted unchanged in the urine.

Melatonin levels vary with age: in newborns during the first three months of life, melatonin levels are low, begin to increase between 3–6 months, reach approximately 65 pg/mL at ages 5–15, and decrease to around 20 pg/mL by ages 50–70. In adults, the average plasma concentration is approximately 50–70 pg/mL [13].

Melatonin secretion is dependent on the photosensitivity of pinealocytes. Light exposure suppresses its synthesis, while in darkness, pinealocytes resume melatonin production. Secretion reaches its peak between 23:00 and 05:00, during which blood concentrations increase 3–10-fold. The circadian rhythm plays a key role in melatonin release: levels begin to rise around 21:00–22:00, peak between 02:00 and 04:00, and decline to basal levels by 05:00–07:00. During the day, plasma concentrations range from 0–20 pg/dL, increasing to 50–200 pg/dL at night. On average, approximately 30 mg of melatonin is synthesized per night [13,14].

Melatonin has antioxidant effects, stimulating antioxidant enzymes, reducing lipid peroxidation, and protecting brain tissue from oxidative damage. It also inhibits the proliferation of cancer cells and the growth of tumors. Melatonin is highly soluble in both water and lipids. As a bioactive compound, it is naturally present in various foods, including oranges, tomatoes, strawberries, grapes, cherries, olive oil, rice, barley, and nuts, as well as in certain medicinal and aromatic plants that serve as pharmaceutical raw materials. Regular consumption of foods rich in melatonin, along with a healthy diet and lifestyle, contributes to the prevention of various pathologies [15].

Effects of melatonin on the immune system

A decrease in melatonin has immunosuppressive effects, reducing both humoral and cellular immune responses. At the end of the 20th century, Maestroni et al. demonstrated that continuous light exposure and β-adrenergic receptor blockade suppressed immune function [16]. Later, Wichmann et al. showed that administration of melatonin restored immune function in studies involving soft tissue injury and hemorrhagic tissues [17].

In rats that underwent pinealectomy, the immune system was suppressed, with thymic atrophy and reduced spleen size. Administration of melatonin orally restored these impairments [18].

A clinical study, individuals who received 10 mg of melatonin orally for 10 days showed an increase in salivary IgA. Another study demonstrated a correlation between urinary melatonin levels and salivary IgA concentrations [19,20]. Through receptors on monocytes and macrophages, melatonin stimulates granulocyte-macrophage colony-stimulating factor and enhances macrophage synthesis. Levels of T-lymphocyte cytokines, including interferon-gamma (IFN-γ), interleukin (IL)-2, IL-6, IL-12, IL-4, and IL-10, are increased, indicating that melatonin helps prevent secondary immunosuppression induced by stress [21].

The effect of melatonin on cancer development

Currently, most studies investigating the effects of melatonin on cancer have been conducted using breast cancer models. Research has shown that administration of melatonin at night yields more favorable outcomes in cancer treatment. A reduction in nocturnal melatonin secretion has been implicated in cancer development. In

particular, women who work under light exposure at night have been found to have an increased incidence of cancer [21].

Antioxidant effects of melatonin

Oxidative stress induced by certain toxins that cause tissue damage can be mitigated by melatonin administration. Because melatonin is soluble in both water and lipid phases, it can easily penetrate all intracellular components, effectively protecting cell membranes, organelles, and the nucleus from free radical-induced damage. Melatonin located on the outer surface of the cell membrane protects it by detoxifying radicals. It also reduces the production of free radicals, such as oxygen (O_2), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH), generated during mitochondrial respiration.

Melatonin protects DNA from oxidative damage, is resistant to oxidation, and does not exhibit pro-oxidant activity. Furthermore, it does not participate in redox cycling or radical-generating reactions [22].

Unlike other antioxidants, melatonin does not exhibit toxic effects even at high doses. Many classical antioxidants (such as vitamin E, vitamin C, and beta-carotene) can act as pro-oxidants after exerting their effects. Although these pro-oxidant byproducts are less harmful than the oxidants they neutralize, they can still cause damage. In contrast, melatonin is an oxidizable compound whose metabolites also retain antioxidant properties. This characteristic is highly valuable for an antioxidant agent and has led to melatonin being described as a “terminal antioxidant.

Effects of melatonin on the cardiovascular system

In vivo studies, intravascular administration of melatonin was found to prevent ventricular tachycardia, ventricular fibrillation, and premature ventricular contractions. Additionally, nocturnal melatonin synthesis may play an important role in lowering blood pressure and heart rate, as well as in the regulation of hypertension [24].

Aging and melatonin

One of the causes of anatomical and functional degeneration observed in organs during aging is a decline in antioxidant capacity and damage from free radicals, as melatonin synthesis decreases with age [25]. Because melatonin stimulates antioxidant enzymes, reduces lipid peroxidation, and protects brain tissue from oxidative damage, its decline contributes to an increase in free radicals, which can lead to various neurodegenerative injuries. Melatonin is an important scavenger of hydroxyl radicals. Loss or reduction of melatonin during aging exposes brain tissue to oxidative attacks, but supplementation with melatonin can help prevent this. Melatonin has been shown to influence immunity, stress response, reproductive physiology, and aging-related processes. A decrease in β-adrenergic receptors on the pineal membrane may lead to reduced melatonin synthesis in the pineal gland, as these receptors mediate norepinephrine release from sympathetic neurons at night, initiating processes that increase nocturnal melatonin production [26].

In pregnant women, melatonin has a beneficial effect on maintaining placental homeostasis until the late stages of pregnancy. Its potent antioxidant and anti-inflammatory properties help reduce oxidative reactions and inflammatory processes [27].

Clinical applications of melatonin

Today, melatonin and its agonists have established a place in clinical practice. Melatonin preparations are available both by prescription and over-the-counter. Melatonin is used for sleep disorders and in the treatment of jet-lag, a syndrome caused by rapid travel across time zones resulting in misalignment of the circadian rhythm [28]. On the other hand, melatonin agonists, such as ramelteon, are indicated for insomnia, while agomelatine is used for depression accompanied by sleep disturbances [28,29]. Currently, melatonin is also applied in areas related to depression, particularly in regulating biological rhythms and sleep. By maintaining the biological circadian rhythm, melatonin regulates numerous biological and physiological processes in the body. It plays a role in cell renewal, strengthening the immune system, and regulating body temperature. Due to its lipophilic properties, melatonin is a highly potent antioxidant, capable of reaching all areas of the body and easily crossing the blood-brain barrier.

Melatonin and the gastrointestinal (GI) system

High concentrations of melatonin are synthesized in the gastrointestinal (GI) tract, particularly in enterochromaffin cells. It has been found that not only the pineal gland but also the enzyme responsible for melatonin synthesis, hydroxyindole O-methyltransferase (HIOMT), and its precursor serotonin are present in enterochromaffin cells of the intestinal mucosa. In the epithelial cells of the duodenum, melatonin enhances protective factors by increasing bicarbonate (HCO_3^-) secretion through MT2 receptors. In addition to its receptor-mediated effects, melatonin also exerts receptor-independent actions in the GI tract. By scavenging free radicals, it demonstrates an inhibitory effect on the development of gastrointestinal ulcers [7].

Effects of melatonin in gastrointestinal diseases

It is known that melatonin is synthesized in significant amounts in the gastric mucosa. Due to its lipophilic properties, immunohistochemical studies suggest that melatonin can penetrate deeply into the mucosa, including the myenteric plexus and muscle layers, potentially exerting effects there [30]. The gastric mucosa is constantly exposed to factors capable of damaging tissues, such as hydrochloric acid and pepsin. Several protective mechanisms exist to preserve the structure and function of the stomach against these factors, including the mucus–bicarbonate barrier and prostaglandins. An imbalance between harmful agents and protective mechanisms leads to gastric injury. In experimental animal models, gastric damage or ulcer formation is induced by various methods such as ethanol or indomethacin administration, restriction of movement, and exposure to cold or stress [30].

Studies conducted in the early 2000s demonstrated that administration of melatonin and L-tryptophan could prevent the formation of gastric ulcers induced by stress and ischemia-reperfusion models. Furthermore, these studies showed that the protective effects of melatonin and L-tryptophan could be abolished by indomethacin administration [31]. Based on these results, it was suggested that the therapeutic and prophylactic effects of melatonin on gastric mucosal injury are mediated through

stimulation of the cyclooxygenase pathway, enhancement of prostaglandin synthesis, and induction of nitric oxide (NO) production. Additionally, melatonin has been shown to accelerate blood flow, which contributes to its protective mechanism. These findings are consistent with studies reporting increased inducible nitric oxide synthase (iNOS) expression and mRNA levels at the margins of existing ulcers in animals [32,33].

The antioxidant effect of melatonin, achieved through scavenging reactive oxygen species, also plays a critical role in its gastroprotective and therapeutic actions. Indeed, in animal studies where cyclooxygenase enzymes and prostaglandin synthesis were inhibited by indomethacin, melatonin still exerted protective and therapeutic effects due to its antioxidant properties. Beyond these mechanisms, there is evidence that treatment with melatonin and L-tryptophan increases gastrin and cholecystokinin concentrations, further contributing to ulcer healing [32-34]. Collectively, these studies support the potential of melatonin and L-tryptophan in treating gastric mucosal injury.

Gastroesophageal reflux disease (GERD), chronic esophagitis, Barrett's esophagus, esophageal strictures, and esophageal cancer are among the prevalent gastrointestinal pathologies in the population. The incidence of Barrett's esophagus and esophageal strictures has been increasing over the years. Consequently, the role of melatonin has been specifically investigated in patients with GERD. Clinical studies have shown that administration of melatonin and L-tryptophan can reduce GERD symptoms and even lead to complete remission [35].

In animal models of GERD, pre-treatment with melatonin was observed to prevent esophageal injury. These studies also demonstrated that melatonin's therapeutic effects are associated with increased blood flow in the gastrointestinal mucosa, enhanced prostaglandin (PGE2) synthesis, and decreased TNF-alpha levels [36]. In patients with GERD and duodenal ulcers, lower plasma melatonin levels were observed, suggesting that melatonin deficiency may contribute to accelerated damage of the upper gastrointestinal mucosa. In elderly populations, reduced melatonin synthesis correlates with an increased risk of complications from reflux esophagitis, indicating that melatonin insufficiency may be a factor in upper gastrointestinal mucosal injury [36,37].

Inflammatory bowel diseases (IBD), primarily Crohn's disease and ulcerative colitis, are chronic inflammatory conditions characterized by relapses and temporary periods of remission. The development of chronic inflammation involves certain genetic predispositions as well as environmental triggers that disrupt the integrity of the intestinal epithelial barrier. Studies have shown that circadian rhythms influence the composition of the gut microbiota, suggesting a possible link between melatonin secretion and the pathogenesis of IBD. Clinical studies indicate that adjunctive administration of melatonin alongside standard therapy significantly improves treatment outcomes in patients with Crohn's disease and ulcerative colitis [38].

Melatonin has been shown to exert protective effects on the intestinal mucosa in animal models of colitis induced by intracolonic administration of acetic acid or 2,4,6-trinitrobenzene sulfonic acid (TNBS). These protective effects are associated with melatonin's ability to reduce the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in the colon [39].

In preclinical studies, treatment of rats with hepatic steatosis using melatonin resulted in reductions in body weight, adiposity index, oxidative stress, and inflammation. However, melatonin did not significantly affect glucose metabolism disturbances induced by a high-carbohydrate diet. Melatonin was observed to slow the progression of non-alcoholic fatty liver disease (NAFLD) through various mechanisms. Long-term administration also improved liver function parameters, including aminotransferases. Regarding its effects on lipid profile, liver aminotransferases, and gamma-glutamyl transpeptidase, melatonin has been suggested as both a potential diagnostic marker and a therapeutic option for managing NAFLD [40,42]. Additionally, higher doses of melatonin reduced the steatosis index in rats fed a high-carbohydrate diet, whereas in healthy rats, high-dose melatonin caused mild liver injury [43,44]. Thus, melatonin treatment demonstrated beneficial effects in NAFLD induced by high-carbohydrate diets in rats. Consequently, due to the potential risk of lipid metabolism disturbances and liver complications, high doses of melatonin should be administered with caution [45,47].

Several clinical and preclinical studies have shown that melatonin synthesized in the intestine plays an important role in improving digestive tract function, particularly in protein digestion and the regulation of gut microbiota [48–52].

In a preclinical study investigating the protective effects of melatonin against hepatocellular aging induced by D-galactose (D-Gal) in rats, liver inflammation, structural damage to hepatocytes, and non-alcoholic fatty liver disease were examined. Rats were divided into four groups: phosphate-buffered saline (PBS, control), D-Gal (200 mg/kg/day), melatonin (20 mg/kg/day, control), and a combination of D-Gal (200 mg/kg/day) with melatonin (20 mg/kg/day). The compounds were administered once daily for eight consecutive weeks. Treatment with melatonin attenuated D-Gal-induced hepatocyte damage. Aminotransferase levels were significantly elevated in the D-Gal groups compared to controls, whereas alanine aminotransferase levels were reduced in the group receiving both D-Gal and melatonin. Inflammatory genes, including IL-1β, NF-κB, IL-6, TNF-α, and iNOS, were significantly upregulated in the D-Gal groups but were markedly lower in the D-Gal plus melatonin group. Furthermore, the expression levels of genes associated with liver steatosis, such as LXRα, C/EBPα, PPARα, ACC, ACOX1, and CPT-1, were significantly reduced in the D-Gal plus melatonin group. These results indicate that melatonin mitigates D-Gal-induced hepatocyte aging and suppresses both hepatic steatosis and inflammation [53]

Conclusion

Overall, research has demonstrated that melatonin is an effective chronobiological molecule capable of acting in multiple directions. Clinical studies have shown positive results regarding the protective effects of melatonin in peptic ulcer disease and in reducing symptoms in patients with gastroesophageal reflux disease (GERD). Several

studies have confirmed its protective role against damage caused by aggressive factors that disrupt the function of the digestive system. Moreover, melatonin has shown beneficial effects in liver pathologies (non-alcoholic fatty liver disease, hepatic steatosis) and intestinal disorders (Crohn's disease, prolonging remission in ulcerative colitis), as well as significant positive outcomes in irritable bowel syndrome. Therefore, its widespread clinical use, particularly due to its mucosa-protective properties, is not surprising. Research continues to explore the role, function, and potential pharmacological effects of melatonin in the gastrointestinal system, and this topic remains highly relevant. Further clinical studies are needed to fully harness the therapeutic potential of melatonin's antioxidant effects across various medical fields.

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