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THERAPEUTIC EFFECTS OF MELATONIN IN AN ETHANOL-INDUCED GASTRIC ULCER MODEL

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Abstract

Introduction. Recently, melatonin and its agonists have been proven to be effective in the treatment of jet lag syndrome, insomnia, stress, fear, anger, anxiety, stress conditions, which are accompanied by sleep disorders, increase the immune system of the whole body, and as antioxidant protection. Melatonin is known to be an important chronobiological molecule that exerts its effect on any system in the body. The role and pharmacological effect of melatonin in the gastrointestinal system is still one of the important topics, and research continues in various directions.

Aim. To monitor the therapeutic effects of melatonin in relation to ethanol concentration in an ethanol-induced experimental gastric ulcer model.

Material's and method. A prospective preclinical (experimental) single-center study. The work was carried out using laboratory rats. The research work was carried out for each of the 6 groups, in a model of gastric ulcer induced by ethanol of various concentrations (100-75-60%) and melatonin was administered to the ulcer (15 mg/kg) and the control group. The obtained data were subjected to statistical analysis using a trial version of the SPSS statistical program (SPSS 20 Inc, Chicago, IL, USA), the critical significance level (p) was assumed to be 0.05.

Results. In addition to this increase in the wound area, melatonin administered as a prophylactic subcutaneous injection reduced the overall wound area. In the group of wounds induced by ethanol (100%), the wound area was 15.01±1.92 mm, after intraperitoneal injection of melatonin (15 mg/kg), and after 30 minutes the wound area was 14.01±1.74 mm in the 100% ethanol-induced group and 13. 24±1.71 mm, in the 75% ethanol-induced group, 11.87±1.45 mm in the melatonin + 75% ethanol-induced group, 11.52±1.15 mm in the 60% ethanol-induced group and 6.12± 0.54 mm in the melatonin + 60% ethanol-induced group.

Conclusion. In this study, melatonin showed a positive effect in the prevention and treatment of ethanol-induced ulcers at different concentrations. A significant change was observed at higher levels of melatonin inhibition of ethanol exposure at lower concentrations.

Keywords: *melatonin, antioxidant, circadian rhythm, metabolic syndrome, digestive system, gastrointestinal ulcer.*

Резюме

ТЕРАПЕВТИЧЕСКИЕ ЭФФЕКТЫ МЕЛАТОНИНА НА МОДЕЛИ ЯЗВЫ ЖЕЛУДКА, ВЫЗВАННОЙ ЭТАНОЛОМ

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Актуальность. В последнее время мелатонин и его агонисты доказали свою эффективность в качестве антиоксидантной защиты при лечении синдрома смены биологических ритмов, бессонницы, стресса, страха, гнева, тревоги, стрессовых состояний, которые сопровождаются нарушениями сна и повышают иммунитет всего организма. Известно, что мелатонин является важной хронобиологической молекулой, оказывающей влияние на любую систему организма. Роль и фармакологический эффект мелатонина в системе желудочно-кишечного тракта до сих пор остается одной из важных тем и исследования продолжаются в различных направлениях.

Цель. Исследование терапевтических эффектов мелатонина в зависимости от концентрации этанола в модели экспериментальной язвы желудка.

Материалы и методы. Проспективное доклиническое (экспериментальное) одноцентровое исследование. Работа проводилась с использованием лабораторных крыс. Исследовательская работа проводилась для каждой из 6 груп, в модели язвы желудка, индуцированной этанолом различной концентраций (100-75-60%) и вводился мелатонин до язвы (15 мг/кг) и контрольной группе. Полученные данные были подвергнуты статистическому анализу с помощью пробной версии статистической программы SPSS (SPSS 20 Inc, Chicago, IL, USA), критический уровень значимости (p) принимался за 0,05.

Результаты. В желудке крыс этанол при макроскопическом анализе в зависимости от концентрации увеличивал площадь раны. Мелатонин вводимый в виде профилактической подкожной инъекции, уменьшал общую площадь раны. В группе индуцированным этанолом (100%), площадь раны без введения мелатонина составила 15,01±1,92 мм., а с введением мелатонина (15 мг/кг) до язвы площадь раны уменшилась на 14,01±1,74 мм., и в группе 75% этанола, площадь раны без введения мелатонина составила 13,24±1,71 мм., введением мелатонина до язвы площадь раны уменшилась на 11,87±1,45 мм., и в группе 60% этанола, площадь раны без введения мелатонина составила 11,52±1,15 мм., и введением мелатонина до язвы площадь раны уменшилась на 6,12 ± 0,54 мм.

Выводы. В этом исследовании мелатонин показал положительный эффект в профилактике и лечении язв, вызванных этанолом, в различных концентрациях. Значительное изменение наблюдалось в более высоких уровнях ингибирования мелатонина при воздействии этанола в более низких концентрациях.

Ключевые слова: *мелатонин, антиоксидант, циркадный ритм, метаболический синдром, пищеварительная система, язва желудочно-кишечного тракта.*

Түйіндеме

ЭТАНОЛМЕН ШАҚЫРЫЛҒАН АСҚАЗАН ЖАРА МОДЕЛІНДЕ МЕЛАТОНИННІҢ ЕМДІК ӘСЕРІ

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Өзектілігі. Қазіргі таңда, мелатонин және агонистерін тек ұйқының бұзылуымен бірге жүретін жетлаг синдромы, ұйқысыздық, стресс, қорқыныш, ашулану, мазасыздық, күйзелістік жағдайларды емдеуде, жалпы ағзаның иммундық жүйесін көтеруде, антиоксиданттық қорғаныс ретінде тиімділігі дәлелденген. Мелатонин организмде кез келген жүйеде әсерін көрсететін маңызды хронобиологиялық молекула екендігі бұрыннан мәлім. Мелатониннің асқазан-ішек жүйесіндегі рөлі және фармакологиялық әсері осы күнге дейін өзекті тақырыптардың бірі болып, түрлі бағыттарда зерттеулер жалғасын табуда.

Зерттеудің мақсаты. Этанолмен шақырылған эксперименталді асқазан жара моделінде этанол концентрациясына байланысты мелатониннің емдік әсерін бақылау.

Зерттеудің материалдары мен әдістері. Проспективті клиникаға дейінгі (эксперименттік) бір орталықты зерттеу. Жұмыс зертханалық егеуқұйрықтарды қолдану арқылы жүргізілді. Зерттеу жұмыстары 6 топтың әрқайсысы үшін әр түрлі концентрациядағы этанолмен индукцияланған асқазан жарасының моделінде (100-75-60%) жүргізілді және мелатонин ойық жараға (15 мг/кг) және бақылау тобына енгізілді. Алынған мәліметтер SPSS статистикалық бағдарламасының сынақ нұсқасында (SPSS 20 Inc, Chicago, IL, USA) талдаудан өтті, статистикалық маңызды деңгейі $p < 0,05$ деп қабылданды.

Зерттеу нәтижелері. Егеуқұйрық асқазанында этанол концентрация тәуелді макроскопиялық талдауда пайда болған жара ауданын арттырды. Осы жара ауданының артуында мелатонин алдын ала профилактикалық мақсатта теріастылық иньекция түрінде берілгенде, жараның жалпы ауданын азайтқан. Этанолмен (100%) шақырылған жара тобында пайда болған жара ауданы 15.01±1.92мм болса, алдын ала мелатонин (15мг/кг) перитон ішіне беріліп, 30 минуттан соң 100% этанолмен шақырылған жара тобында 14.01±1.74 мм, 75% этанол тобында 13.24±1.71 мм болса, мелатонин+ 75% этанолмен шақырылған жара тобында 11.87±1.45 мм, 60% этанолмен шақырылған жара тобында 11.52±1.15 мм болса, ал мелатонин+ 60% этанолмен шақырылған жара тобында 6,12±0,54 мм жара ауданы азайғандығы байқалған.

Қорытындылары. Осы зерттеуде әр түрлі концентрацияда этанолдан пайда болған жараның алдын алуда, емдеуде мелатонин оң әсерін көрсеткен. Неғұрлым төмен концентрациядағы этанолдың әсеріне мелатонин жараның алдын алуда соғұрлым жоғары деңгейде мәнді өзгеріс байқалған.

Түйінді сөздер*: Мелатонин, антиоксидант, циркадты ырғақ, метаболикалық синдром асқорыту жүйесі, асқазан-ішек жолдарының жара ауруы.*

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Introduction

Melatonin is a natural neurotransmitter involved in the regulation of many biological and physiological processes, sleep, and biorhythms (circadian rhythms) in the body. Its main task is to control the body's biological clock and to maintain its rhythm [8]. Melatonin (chemical name 5-methoxy N-acetyl tryptamine) is an indole hormone secreted mainly by the pineal gland and synthesized by other peripheral systems such as the brain, bone marrow, platelets, lymphocyte cells, and skin, and affects many systems [12-16]. its effects on cell regeneration and the immune system, as well as other known functions, are known. This literature review discusses the role of melatonin synthesized in the gastrointestinal (GI) tract for the body and its effects on physiological and pathological processes, focusing on the general characteristics of the hormone melatonin. Melatonin is synthesized from enter chromaffin cells in the gastrointestinal tract, with the intensity of this synthesis coordinated with the rhythm of food intake. The concentration of melatonin in the gastrointestinal tract is about 10-100 times that in blood. In fact, the total amount of melatonin in the gastrointestinal mucosa is 400 times greater than in the pineal gland [18-19].

Synthesis of the hormone melatonin. Tryptophan, a precursor for the synthesis of melatonin, an essential amino acid, is obtained from food. After the removal of tryptophan from the plasma through the pineal gland, 5-hydroxytryptophan, the first intermediate for the synthesis of serotonin and melatonin, is formed in pinealocytes by hydroxylation with tryptophan hydroxylase and easily passes the blood-brain barrier. Using the enzyme tryptophan hydroxylase, tetrahydrobiopterin (BH4) and superoxide (O2), and vitamin B6 as coenzymes, 5-hydroxytryptophan is converted into 5-hydroxytryptamine (serotonin) by the enzyme 5-hydroxytryptophan decarboxylase. Serotonin cannot cross the blood-brain barrier. Serotonin and is then acetylated with N-acetylserotin by the enzyme N-acetyltransferase (NAT). N-acetyl serotonin combines with HYOMT (hydroxyl indole methyltransferase) to N-acetyl 5-methoxy tryptamine, i.e. it is converted to melatonin [3-5].

Sites of synthesis of the hormone melatonin. In mammals, melatonin is secreted by the pineal gland, the biliary and gastrointestinal tracts, the pigment epithelium, and retinal photoreceptors and plays a role in regulating the retinal response to the change of day and night. Melatonin, produced in the skin, is responsible for tissue changes and protection against harmful sunlight.

After a meal, melatonin, which is synthesized by the chromaffin cells of the gastrointestinal tract, is released into the bloodstream. Melatonin is synthesized in the bile-oxidized cholesterol derivatives and protects the mucous layer and epithelium of the bile ducts from oxidative damage by bile acids. However, this synthesized amount has very little effect on circulating melatonin levels. The amount of melatonin in the circulating pineal gland synthesizes is about 80% [1,6, 9].

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 responsible for the retina, kidney function, biological rhythm, fertility function and contraction of cerebral arteries [2]. On the other hand, MT2 and MT3 receptors act by hydrolyzing phosphoinositol. Melatonin receptors are found in various parts of the human brain, intestine, ovaries and blood vessels. Known agonists are used for sleep disorders and depression: the melatonin analogue rameolton, tasimelteon, agomelatine [11-12].

Pharmacokinetics. Melatonin binds 60-70% to albumin in the blood. The elimination half-life of melatonin is 3-45 minutes. Melatonin, which is partially contained in water and lipids in large quantities, is easily absorbed into tissues and cells. Melatonin is first converted in the liver to 6-hydroxy dopamine and then to N-acetyl-5-methoxy-6-hydroxytryptamine via a series of reactions. It is then converted to 6-sulphatoxymelatonine, conjugated to sulfate or glucuronide, and excreted in the urine. 1% is excreted unchanged in the urine. Because of age, melatonin levels are low in newborns during the first three months of life. 65 pg/ml at 5 to 15 years of age, 20 pg/ml at 50 to 70 years of age. In adults, average plasma levels are 50-70 pg/ml [23].

Melatonin hormone secretion is dependent on the photosensitivity of pinealocyte cells, light causes synthesis to slow down, and in darkness, and melanocytes begin to secrete melatonin again. Melatonin secretion is highest between 23:00 and 05:00, and the concentration in the blood increases by a factor of 3-10. The release of melatonin has a specific circadian rhythm. It starts increasing in the evening at 21:00-22:00 and peaks at 02:00-04:00. It begins to decrease at 05:00-07:00 in the morning. It starts after 07.00 and decreases to basal levels. The blood concentration of melatonin is 0-20 pg/dl during the day and rises to 50-200 pg/dl at night. An average of 30 mg of melatonin is synthesized during the night [7,10].

The antioxidant effect of melatonin. Oxidative stress caused by certain toxins, which cause oxidative damage to

tissue, is stopped by melatonin. As melatonin is water- and lipid-soluble, it easily penetrates into all intracellular components and effectively protects the cell membrane, organelles, and nucleus from free radical damage. Melatonin on the outer surface of the cell membrane protects the cell membrane by detoxifying free radicals. Oxygen (O2), hydrogen peroxide (H2O2), and hydroxy (OH) formed during mitochondrial respiration reduce the release of free radicals.

Provides protection against the oxidation of DNA, molecule is not easily oxidized due to its lack of peroxidation activity. In addition, it does not enter the redox cycle and radical forming reactions [20]. Unlike other antioxidants, it has no toxic effect when used in excessive amounts. The various classic antioxidants (vitamin E, vitamin C, beta-carotene, etc.) become pro-oxidants once they show their action. These substances are less harmful than the oxidants they remove. However, melatonin is an oxidant, and its by-products also have antioxidant effects. Its property is very valuable for an antioxidant agent and is described as a 'terminal antioxidant. In conclusion; Melatonin has been found to stimulate antioxidant enzymes, prevent lipid peroxidation, and protect brain tissue from free radicals produced by oxygen intake [21-22].

Melatonin and the digestive system. Melatonin is synthesized in high concentrations in enter chromaffin cells of the gastrointestinal tract. Not only the epiphyseal enzyme of melatonin synthesis hydroxyl-O-methyltransferase (HIOMT) and its precursor serotonin are found in enter chromaffin cells of the intestinal mucosa. Increases bicarbonate (HCO3) secretion via melatonin receptors (MT2) in duodenal epithelial cells and enhances the protective factor.

Melatonin acts in the digestive system in addition to its receptor effect as well as in a non-receptor way. By removing free radicals, GI has an inhibitory effect on ulcer formation [24].

Effects of melatonin on digestive diseases. Melatonin is known to be synthesized in significant amounts in the gastric mucosa. Because of its lyophilic properties, the results of immunohistochemically studies support the hypothesis that it can penetrate deeper into the mucosal layer, even into the intermuscular plexus, and into the muscular layers [28]. The gastric mucosa is constantly exposed to factors such as hydrochloric acid and pepsin, which can damage the tissue. There are many mechanisms that protect the structure and function of the stomach against these factors, such as the mucosal bicarbonate barrier and prostaglandins. An imbalance between the harmful agents and the protective mechanisms causes damage to the stomach.

Gastric damage or ulceration has been induced in experimental animal studies by various means, such as ethanol administration, injection of indomethacin, exercise restriction, and cold stress [25]. Studies carried out in the early 2000s showed that stress-induced gastric ulcer formation in an ischemia-reperfusion model was suppressed by the administration of melatonin and L-tryptophan. These studies have suggested that the therapeutic and prophylactic effects of melatonin on gastric mucosal damage are based on stimulation of the cyclooxygenase pathway, an increase in prostaglandin synthesis, and induction of nitric oxide (NO) synthesis. It has also been shown to accelerate blood flow in the mechanism of action.

These results are consistent with studies showing an increase in inducible nitric oxide synthase (iNOS) mRNA and its expression at the edges of healing ulcers [26,27].

The role of the antioxidant effect of melatonin through the removal of reactive oxygen species in this protective and therapeutic effect cannot be excluded. In fact, animal studies in which cyclooxygenase enzymes and prostaglandin synthesis are inhibited by indomethacin have shown that melatonin has therapeutic and protective effects due to its antioxidant activity.

In addition to all these effects, there is evidence that the increased concentrations of gastrin and cholecystokinin observed in patients treated with melatonin and L-tryptophan also promote ulcer healing [29-31]. In light of these studies, the ability of melatonin and L-tryptophan to treat gastric mucosal damage can be summarized. Other important pathologies such as gastroesophageal reflux disease (GERD), chronic esophagitis, Barrett's esophagus, and esophageal cancer are common in the community. The incidence of Barrett's esophagus and esophageal strictures is increasing. For this reason, the effect of melatonin in patients with gastroesophageal reflux disease has been specifically studied. One of these, melatonin and L-tryptophan, has been clinically tested for reducing the symptoms of gastroesophageal reflux disease and achieving complete remission [32]. In an animal model of gastroesophageal reflux disease, prior administration of melatonin prevented esophageal damage. In the same study, it was shown that increased mucosal blood flow, increased prostaglandin synthesis (PGE2), and decreased TNF-alpha levels were associated with a therapeutic effect of melatonin [33]. Reduced plasma melatonin levels in patients with digestive diseases, such as gastroesophageal reflux disease and duodenal ulcer disease, have shown that deficiency of this hormone influences the rapid damage of the upper gastrointestinal mucosa. Reduced melatonin synthesis in the elderly patient group and a higher risk of complications due to reflux esophagitis in elderly patients support the possibility of a possible harmful effect of melatonin deficiency on upper gastrointestinal mucosa [33,34].

Inflammatory bowel diseases, more commonly Crohn's disease and ulcerative colitis, are chronic inflammatory pathologies with remissions with relapses and temporary improvements. Triggers are also the occurrence of chronic inflammation, the presence of some genetic predisposition, and environmental factors that compromise the integrity of the intestinal epithelial barrier. There are studies that show that circadian rhythm influences the composition of the intestinal microbiota. There may be a hypothetical link between inflammatory bowel disease and melatonin secretion. A clinical trial reported that melatonin significantly improved outcomes in Crohn's disease and ulcerative colitis when prescribed in addition to basic treatment for inflammatory bowel disease [25].

By reducing the expression of melatonin-induced nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in the colon, acetyl acid enemas with 2,4,6-trinitrobenzene sulphonic acid (TNBS) have been shown to have a

protective effect on the intestinal mucosa against models of induced colitis [26].

The role of melatonin in clinical use. Today, melatonin and its agonists have found use in clinical practice. Melatonin medications are available with or without a prescription. Melatonin is used for sleep disorders, a syndrome of circadian rhythm disturbance due to short journeys called 'jetlag' [27]. On the other hand, drugs such as ramelteon, which are melatonin agonists, are indicated for insomnia, and agomelatine is indicated for depression associated with sleep disorders [28,29]. Current applications of melatonin are depression, including biological rhythm and sleep regulation.

Aim. To monitor the therapeutic effects of melatonin in relation to ethanol concentration in an ethanol-induced experimental gastric ulcer model.

Materials and methods

Study: Experimental (preclinical). Preclinical model details.

Subjects: Wistar Albino rats (300–380 g).

Induction of Ulcers: Gastric ulcers induced using ethanol at varying concentrations (100%, 75%, 60%). This concentrations of ethanol through a special gastric probe and waited for 1 hour to develop an ulcer model.

Groups: group 1: Ethanol-only (control). n=6;

group 2 (pre – melatonin): Ethanol + melatonin (15 mg/kg) administered intraperitoneally. Melatonin (15 mg/kg) was administered intraperitoneally before 30 min ethanol consumption. n=6;

group 3 (pre – melatonin): Control group. Melatonin (15 mg/kg) was administered intraperitoneally before 30min euthanasia n=6;

Melatonin dosage: Administered intraperitoneally at 15 mg/kg.

Outcome Measures: Macroscopic analysis of gastric lesions (ulcer area).

Etics approval. Approval for the research was received from Gazi University Animal Experiments Local Ethics Committee (Number: 04.10.2019-E.123689).

The study was conducted in group 6, with models of gastric ulcer induced by ethanol in different concentrations (100-75-60%) and pre-melatonin (15 mg/kg) administered intraperitoneally in the ulcer group and control group. This preclinical study was conducted in the research laboratory of the Department of Clinical Pharmacology, Faculty of Medicine, Gazi University, Turkey. Ethanol-induced gastric ulcer model Rats weighing 300-380 g, matured under standard conditions (Wistar Albino breed), were injected with different concentrations of ethanol through a special gastric probe and waited for 1 hour to develop an ulcer model. Subsequently, euthanasia was carried out under anesthesia, the stomach was extracted and macroscopic analysis was performed\ The wound area was measured using a millimeter ruler. Statistically, variables were summarized using frequencies and percentages. P <0.05 was considered statistically significant.

The results

In the rat stomach, ethanol increased the wound area in a concentration-dependent macroscopic analysis. In addition to this increase in the wound area, melatonin administered as a prophylactic subcutaneous injection reduced the total wound area. In the ethanol-induced group (100%), the wound area was 15.01±1.92 mm, with melatonin (15 mg/kg) administered intraperitoneally, and the wound area was 14.01±1.74 mm after 30 minutes in the 100% ethanol-induced group, 13.24±1.71 mm in the 75% ethanol group, 11.87±1.45 mm in the melatonin + 75% ethanol induced group, the wound area was 11.52±1.15 mm in the 60% ethanol induced group and 6.12±0.54 mm in the melatonin + 60% ethanol induced group [Table 1; Figure 1,2].

Table 1.

Effects of melatonin in a model of gastric ulcer induced by ethanol at different concentrations.

Concentration	n	Macroscopic wound area	Concentration	n	Macroscopic wound area
Ethanol 100%	6	15.01±1.92	Melatonin + Ethanol %	6	14.01±1.74
Ethanol 75%	6	13.24±1.71	Melatonin + Ethanol 75%	6	11.87±1.45
Ethanol 60%	6	11.52±1.15	Melatonin + Ethanol 60%	6	6.12±0.54

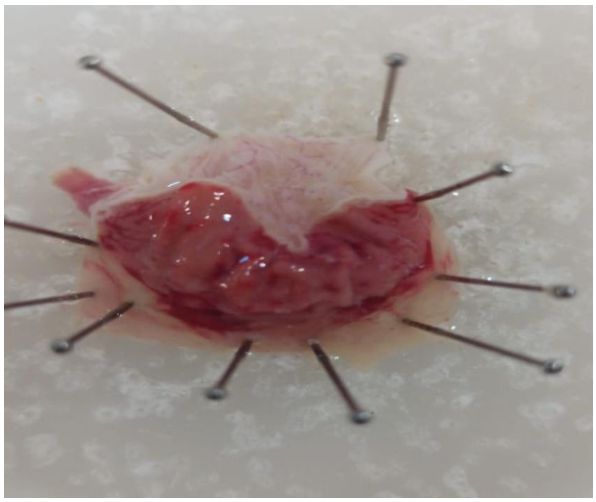

Figure 1. Model of an ethanol-induced gastric ulcer.

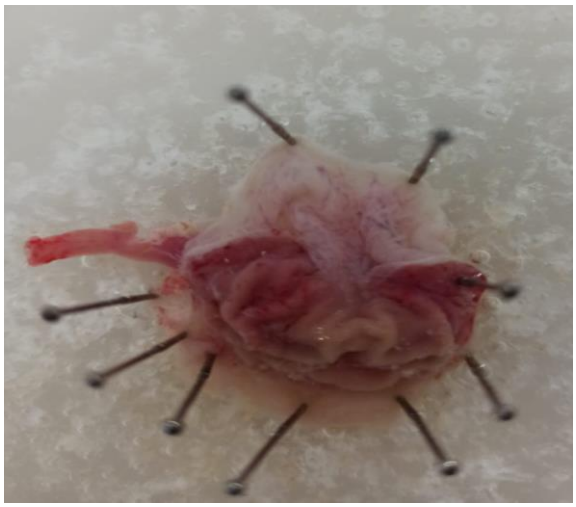

Figure 2. Melatonin + ethanol gastric ulcer model.

Rats in the control group were put to sleep by anesthesia after 24 hours of fasting without any manipulation. In the control group, no signs of gastric mucosal lesions were observed when the gastric mucosa was analyzed. 1 h after administration of ethanol through the gastric tube, the mucosa of the group which developed gastric ulcer showed erosions, ulcers, hemorrhages, petechial with black spots, puffiness, swelling of the mucosa, and an area of lesions with redness. 1 hour later. 30 min after intraperitoneal injection of melatonin (15 mg/kg) in rats administered ethanol via a gastric tube, the mucosal layer showed erosions, reduced ulcerated area, pulmonary petechial, edema, the reddening area of the mucosal layer was statistically reduced compared with the wound model group, and no bleeding was observed.

Discussion

A single blind randomized study was performed in which 176 patients underwent treatment using the supplement cited and 175 received treatment of 20 mg omeprazole. All patients with melatonin (100%) reported a complete regression of symptoms after 40 days of treatment. On the other hand, 115 subjects (65.7%) of the omeprazole reported regression of symptoms in the same period. There was statiscally significant difference between the groups ($P < 0.05$). This formulation promotes regression of GERD symptoms with no significant side effects [22].

In a gastric ulcer model, it has been shown that prior administration of melatonin through the gastric tube reduces the area of ulcer formation. In many experimental and clinical studies, melatonin pre-injection has been shown to reduce pathological and inflammatory processes in various models of the digestive system. When the ethanol concentration is high, the wound area is enlarged and bleeding is more severe, while in the groups receiving lower concentrations, the wound area is relatively reduced compared to the 100% concentration. The therapeutic properties of melatonin depend on the concentration of ethanol. In other words, melatonin exhibited a therapeutic effect to varying degrees, depending on the strength of the aggressive factor. Particularly in the group of wounds induced by 60% ethanol, the therapeutic protective effect of melatonin was statistically significant. Melatonin has been shown in many studies to reduce ulcer index and lesion area in a model of gastric ulcer induced by other factors such as ethanol, stress, indomethacin, and non-steroidal anti-inflammatory drugs. It has been suggested that the mechanism of action lies in the stimulation of nitric oxide and prostaglandin synthesis. In addition, melatonin has been shown to exert its effects by increasing mRNA levels and the expression of inhibitory nitric oxide synthase (iNOS) in the tissue surrounding the wound. In a model of gastroesophageal reflux disease, its beneficial and protective effects on the esophageal mucosa were attributed to its antioxidant and anti-inflammatory effects. It has been shown to reduce the secretion of pro cytokines involved in inflammation, such as IL-1beta and TNF-alpha [29-31].

Application of melatonin abrogates mesothelial cell pyroptosis through a MT1R-mediated action, and successfully reduces peritoneal fibrosis and angiogenesis in an animal model while preserving dialysis efficacy. Mechanistically, melatonin treatment maintains mitochondrial integrity in mesothelial cells, meanwhile activating mTOR signaling through an increase in the glycolysis product dihydroxyacetone phosphate [32].

In a clinical trial, the use of melatonin alone and in combination with omeprazole in 36 patients diagnosed with gastroesophageal reflux disease showed very significant results in reducing complaints [33].

Conclusion

Melatonin is known to be an important chronobiological molecule that exerts its effect on any system in the body. The role and pharmacological effect of melatonin in the gastrointestinal system is still one of the important issues, and research continues in various directions. In this study, melatonin showed a positive effect in the prevention and treatment of ethanol-induced ulcers at different concentrations. A significant change was observed at higher levels of melatonin inhibition of ethanol exposure at lower concentrations. We hope that in clinical practice, taking into account its therapeutic effect on the mucous membrane of the digestive system through its antioxidant effect against oxidative stress, and taking into account the preventive and therapeutic properties of the digestive system, the indicator of wide-spectrum use will increase. For this reason, it is necessary to conduct clinical studies in different directions for the use of its antioxidant effect.

Etics approval.

Approval for the research was received from Gazi University Animal Experiments Local Ethics Committee (Number: 04.10.2019-E.123689).

***Authors' contributions** (распишите Фамилию и инициал)*

Concept: Skenderova A.A., Nuskabayeva G.O., Tatykayeva U.B., Sarsenbayeva G.Zh., Kemelbekov K.S., Seidakhmetova A.A.,

Final approval: All listed authors.

This study was presented at the 26th National and 1st International Pharmacology Congress [34].

***Conflicts of interest:** All authors declare no conflict of interest.*

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