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Cardioprotective effect of melatonin on ischemic heart disease clinical course in elderly patients with insomnia

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Abstract

We aimed at studying the exogenous melatonin corrective effect on Ischemic heart disease (IHD) clinical features in elderly patients with sleep disorders. A total of 60 patients aged from 60 to 74 with IHD, angina pectoris functional class (FC) II and complaints of sleep disorder were examined. Patients of the 1st group (n = 30), received basic therapy: acetylsalicylic acid, atorvastatin and metoprolol succinate. A chemical melatonin analogue once a day was added to the basic treatment regimen of patients of the 2nd group (n = 30). Timely correction of melatonin pathogenetic deficiency in elderly IHD patients with insomnia by including its pharmacological analogues in the treatment regimen manifests significant improvement in the patients` clinical condition. This is evidenced by the following: a decrease in anginal attacks frequency, dynamics in Holter electrocardiographic study (ECG) monitoring indicators and somnological characteristics.

***Keywords*:** Ischemic heart disease, Melatonin, Insomnia

1. Introduction

Cardiovascular diseases (CVD) are still an urgent problem of our time. They do enormous economic damage to the health care system because of their high mortality proportion worldwide [1]. IHD and cerebrovascular diseases still occupy a leading position in the mortality structure [2], which emphasizes the problem`s global medical and social significance. In Russia mortality caused by these diseases in 2019 amounted to 633 cases per 100 thousand people, while the IHD proportion is 28.4%, according to Rosstat [3]. In the United States, more than 900,000 people die and / or suffer myocardial infarction annually due to IHD chronic forms [4]. Search for additional cardiovascular risk factors and development of new methods for CVD prevention and treatment should help reduce IHD incidence and, consequently, the mortality rate.

An increasing amount of data has recently proved the relationship between IHD and sleep disorders [5,6]. Insomnia prevalence in patients with IHD is significantly higher than in the general population. Thus, the research by Bang Zheng`s team showed a 22% greater risk of IHD development in patients with severe sleep disorders compared with people without insomnia [5].

Sleep disorders in IHD patients can be associated with a low level of norepinephrine [7], a high level of fibrinogen and inflammatory cytokines [8]. Neuroendocrine dysregulation metabolic consequences, prothrombotic disorders associated with atherothrombosis development significantly contribute to the importance of cardiovascular risk factors such as dyslipidemia, obesity, diabetes mellitus in patients with insomnia and IHD [9,10].

Insomnia is characterized by dissatisfaction with sleep quality and quantity and is manifested by difficulties with falling asleep and maintaining sleep, daytime sleepiness, frequent night or early morning awakenings [11], especially in the elderly [12]. It is this age category that is especially sensitive to somnological disorders due to physiological decrease in the melatonin level connected with aging. Therefore, melatonin derivatives are used in clinical practice to correct and synchronize circadian rhythms, improve sleep quality and duration [13].

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced by the pineal gland exclusively at night [14]. Exogenous melatonin supplements are well tolerated and do not have obvious short-term or long-term side effects [13]. Recent studies show its pronounced antioxidant, anti-inflammatory property [15,16] and angioprotective

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action [17]. This allows to consider melatonin and its medicinal analogues as additional agents in treatment of various CVDs and metabolic syndrome [15,18]. Taking into account the relationship between atherosclerotic diseases and sleep disorders, as well as their high incidence in the older age group, we aimed at studying the exogenous melatonin corrective effect on IHD clinical features in elderly patients with sleep disorders.

2- Materials and Methods

On an outpatient basis, 60 elderly patients aged from 60 to 74 with IHD, angina pectoris FC II and complaints of sleep disorder were examined (39 men, 21 women; average age - 68.9 ± 4.3 years). At the time of inclusion in the study, the IHD average duration in the subjects was 4.8 ± 0.8 years, of insomnia - 11.5 ± 1.6 months. Prior to the study and after 6 weeks, all patients underwent a general clinical examination. IHD and angina pectoris FC II were diagnosed in accordance with the Russian National Guidelines for the management of patients with stable angina based on clinical and medical history (complaints of angina attacks during walking, after eating or in the cold, or during emotional stress, or in the first several hours after waking up, while walking > 200 m on flat terrain or while more than one flight climbing stairs at an average pace under normal conditions), laboratory tests (fasting glucose and lipid levels, including total cholesterol, low and high density lipoproteins, triglycerides, complete blood count including haemoglobin and leukocyte formula, creatinine level and routine urine sample) and instrumental examination (ECG, stress samples and Holter ECG monitoring (BTL cardioholter, UK) with an assessment of dominant rhythm, average number of ischemic episodes, duration and degree of ST segment depression or elevation, dominant heart rate (HR), rhythm and conduction disorders). Synchronized circadian heart rhythm assessment was performed using the circadian index (CiI). An increase in CiI > 1.5 was associated with increased sensitivity of heart rhythm to sympathetic stimulation, a decrease in CiI < 1.2 - with heart “denervation" and a high risk of sudden death. Sleep disorders severity in elderly patients was assessed with somnological questionnaires: “Subjective assessment of sleep characteristics” (A.M. Vein, Ya.I. Levin) [19], “The insomnia Severity Index (ISI)” (C. Morin) [20], as well as the Epworth Sleepiness Scale (ESS) [21].

In order to determine the corrective drug therapy effectiveness, all IHD patients were randomized into 2 groups. Patients of the 1st group (n = 30; 18 men and 12 women aged 68.2 ± 4.8 years), received basic therapy in accordance with the current National Clinical Recommendations for stable angina diagnosis and treatment: acetylsalicylic acid (class I recommendations with evidence level A), atorvastatin (class I recommendations with evidence level A) and metoprolol succinate (class I recommendations with evidence level A). A chemical melatonin analogue once a day at a dose of 3 mg 30 to 40 minutes before a night (physiological) sleep was added to the basic treatment regimen of patients of the 2nd group (n = 30; 21 men and 9 women aged 69.5 ± 3.7). Since β-adrenergic blocking agents (β-AB) tend to suppress melatonin physiological secretion exacerbating existing sleep disturbances, at the study start β-AB was prescribed to all patients in the morning.

Statistical analysis was carried out in accordance with the goal. To assess the variables distribution normality, the Kolmogorov-Smirnov test was used. For numerical variables the following values were calculated: mean and standard deviation (M ± s.d) and 95% confidence interval (CI). Also, taking into account the normal sample distribution the Student t-test was used. For statistical analysis the SPSS 22 program (SPSS Inc, USA) for Windows (Microsoft Corporation, USA) was used, and $p < 0.05$ was considered statistically significant.

3- Results

The obtained results made it possible to detect positive dynamics during therapy in both comparison groups. However, therapy with melatonin inclusion in the regimen had obvious advantages and was more effective. The patients` clinical and functional indicator dynamics showed an increase in the level of tolerance to normal physical activity. This was evidenced by an increase in the number of people with angina pectoris FC I in the 1st group to 46.7%, while in representatives of the 2nd group - by 56.7% ($p < 0.05$). Moreover, angina attacks frequency in patients taking melatonin as part of complex therapy decreased by 48.8% (from 3.20 ± 0.6 times to 1.64 ± 0.7 per week; $p < 0.05$), while in patients receiving basic therapy - by 31.3% (from 3.04 ± 0.8 times to 2.06 ± 0.5 per week; $p < 0.05$). An inter-group comparison did not show significant differences. (Table 1).

Achieving the target HR was observed in 83.3% of patients taking melatonin as part of complex therapy and in 73.3% of patients without adaptogen inclusion in the regimen. So, according to Holter ECG data, in patients of the1st group daily HR decreased by 8.0% (from 74.4 ± 1.8 to 68.6 ± 1.0 beats / min), average HR at night- by 7.9% (66.4 ± 1.8 to 61.5 ± 1.6 bpm), while in patients of the 2nd group - by 10.6% and 18.5%, respectively.

	1st group				2nd group			
	Initially		After 6 weeks		Initially		After 6 weeks	
	M ± s.d	95 % CI	M ± s.d	95 % CI	M ± s.d	95 % CI	M ± s.d	95 % CI
Average day HR, bpm	74,4±1,8	72,9-76,1	68,6±1,0*	67,8-69,4	74,6±1,7	73,3-76	67,5±1,5*	66,2-68,8
Average night HR, bmp	66,4±1,6	65,1-67,7	61,5±1,8*	60-62,8	65,9±1,5	64,7-67,3	55,6±1,0*ᴧ	55,3-56,4
HRmin, bmp	56,1±1,3	54,9-57,2	53,4±1,4*	52,3-54,5	55,6±1,1	54,7-56,5	52,4±0,9*	51,9-53,2
HRmax, bmp	115,7±4,7	112,8-117,4	98,6±6,1*	94,2-101,9	116,5±7,3	110,4-120,1	98,2±2,5*	96,4-99,3
Circadian index	1,22±0,03	1,21-1,23	1,21±0,05	1,2-1,24	1,21±0,04	1,19-1,23	1,23±0,02*	1,22-1,24
Diurnal SVES	168,6±45,4	126,2-211,5	109,2±37,6*	73,3-144,7	134,6±39,7	97,8-171,2	88,2±33,6*	56,1-119,6
Diurnal VES	117,0±45,6	76,9-157,1	52,8±13,8*	43,4-63,1	159,0±58,6	103,5-213,7	76,8±18,3*ᴧ	61,7-92,3
QTmax, ms	414,7±38,7	380,4-443,7	461±44,9	419,6-501,9	398±41,3	365,3-436,1	458±50,5	411,5-505,3
STmax elevation, mV	0,18±0,03	0,16-0,2	0,16±0,02	0,14-0,17	0,17±0,04	0,15-0,21	0,15±0,03	0,12-0,16
Duration max, min	2,0±0,6	1,5-2,4	0,96±0,4*	0,58-1,27	2,2±0,8	1,6-2,6	0,84±0,5*	0,49-1,3
STmax depression, mV	0,14±0,05	0,12-0,17	0,12±0,04*	0,1-0,14	0,14±0,04	0,13-0,17	0,11±0,07*	0,07-0,15
Duration max, min	3,1±2,5	1,1-5,1	1,5±1,0*	0,8-2,3	3,0±2,4	1-4,9	1,4±0,9*	0,9-2
Angina attacks frequency per week	3,04±0,8	2,7-3,75	2,06±0,5*	1,66-2,43	3,20±0,6	2,6-3,73	1,64±0,7*	1,05-2,27

Table 1: Holter ECG monitoring dynamics in IHD patients during therapy
Note: * - differences compared to the original data at p <0.05; ᴧ - differences between groups 1 and 2

Inter-group differences reached statistically significant criteria according to average HR in the night period (Table 1).

The use of melatonin also had a significant positive effect on the myocardium electrophysiological activity. So, by the end of the 6th week of treatment, there was a significant decrease in the number of supraventricular extrasystoles (SVES) by 34.5% (p = 0.002) and ventricular extrasystoles (VES) by 51.7% (p = 0.003). The inter-group differences reached the validity criterion according to the VES dynamics (Table 1). It is noteworthy that according to the ECG results at the end of the study, the PQ interval duration varied within the normal range from 119 to 167 ms (average - 129.5 ± 18.8 ms) and the QT interval - from 366 to 437 ms (average 416.7 ± 19.8 ms) .This confirmed absence of the proposed treatment regimens adverse effect on atrioventricular conduction and electrical systole of the heart (depolarization and repolarization processes).

Melatonin addition to the basic therapy had a positive effect on important sleep characteristics (its duration, number of dreams, morning awakening quality), which was shown by the total final assessment, while the falling asleep time and the morning awakening quality had inter-group differences (Table 2). In addition, at the end of the observation period representatives of the 2nd group showed a CiI positive dynamics and an increase in the proportion of patients with normotonia by 30% (up to 66.7% from 46.7% of the initial), which indicates the melatonin synchronizing effect on circadian biorhythms in elderly IHD patients. ISI dynamics was observed in patients of both groups. So, in patients of the 1st group the average ISI score significantly decreased by 8.0% (from 20.3 ± 3.6 to 18.5 ± 2.8) and in patients of the 2nd group - by 10.6% (from 20.2 ± 3.7 to 15.9 ± 2.4), while the inter-group differences reached the statistical significance criteria (Table 2).

Table 2: Dynamics of IHD patients` somnological parameters depending on treatment regimens (in points)

	1st group 1				2nd group			
	Initially		After 6 weeks		Initially		After 6 weeks	
	M ± s.d	95% CI	M ± s.d	95% CI	M ± s.d	95 % CI	M ± s.d	95 % CI
Falling asleep time, score	2,0±0,7	1,5-2,5	2,2±0,9	1,4-2,9	1,9±0,8	1,4-2,5	2,4±0,7*^	1,9-3
Sleep duration, score	1,9±0,6	1,6-2,3	2,5±0,5*	2,3-2,8	1,8±0,7	1,4-2,3	2,7±0,8*	2,1 - 3,3
Number of night awakenings	2,7±1,0	1,9-3,5	3,1±0,8	2,5-3,7	2,7±0,7	2,1-3,3	3,3±1,1	2,6-4
Sleep quality	2,4±0,9	1,7-3,1	2,6±1,0	1,9-3,4	2,4±0,9	1,6-3,2	3,2±0,8*^	2,6-3,9
Number of dreams	1,8±0,6	1,3-2,2	2,3±0,6*	1,9-2,8	1,8±0,7	1,2-2,3	2,5±0,6*	2,2-2,9
Morning awakening quality	1,8±0,9	1,1-2,5	2,0±1,0	1,2-2,6	1,7±0,9	1-2,4	2,4±0,6*^	2,1-2,9
Questionnaire total score	10,1±2,0	8,5-11,6	14,7±2,2*	12,9-16,4	10,5±2,1	8,6-12,1	16,9±1,9*^	15,3-18,4
Average ISI, score	20,3±3,6	17-23,3	18,5±2,8*	16,1-20,9	20,2±3,7	16,8-23,1	15,9±2,4*^	13,8-17,7
Epworth Daytime Sleepiness Scale	6,7±2,7	4,2-9,1	5,3±1,9*	3,6-7	6,9±2,1	5,2-8,7	6,6±1,7^	5,1-7,9

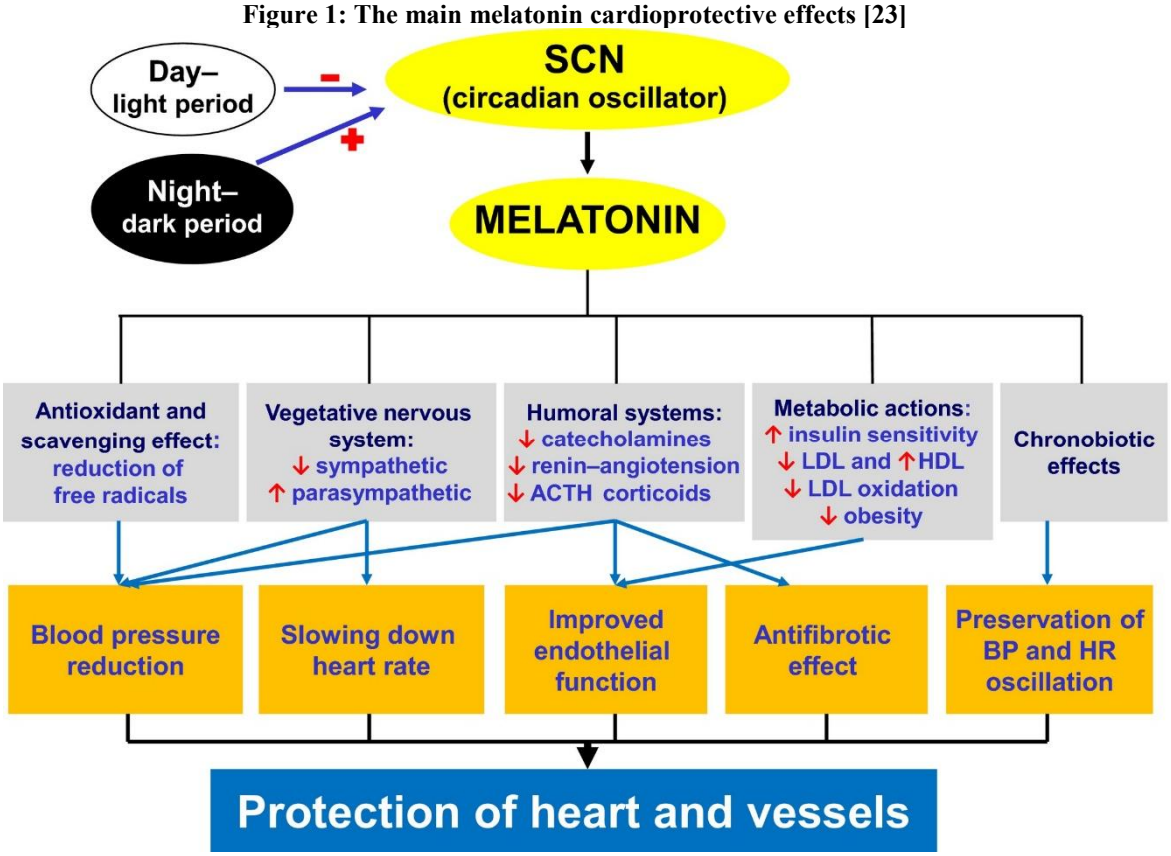
*Note: * - differences compared to the original data at p <0.05; ^ - differences between groups 1 and 2*

Of particular interest was assessment of therapy effect in combination with β-AB. Holter ECG monitoring results did not reveal a significant increase in HR during sleep at the end of the observation period, which was confirmed by respondents` questionnaires. It is important to emphasize good tolerance of the therapy and absence of any side effects while taking medications.

4- Discussion

Recently completed studies by scientists from different countries have established a direct relationship between somnological disorders and IHD development [5,6]. When studying this association, Madsen MT et al. described a direct correlation of sleep disorder severity and IHD development [6]. In IHD patients there is a pathogenetic decrease in the circulating melatonin concentration that depends on the IHD stage [22,23]. There is no doubt that this particular endogenous hormone plays a decisive role in various cardiovascular pathophysiological processes (Fig. 1). Of course, a significantly pronounced decrease in angina attacks frequency observed in patients of both groups was determined by the β-AB metoprolol succinate action. However, statistical differences in the inter-group ECG parameters and Holter ECG monitoring indicated a more significant effect of combined treatment regimen with melatonin inclusion,

Figure 1: The main melatonin cardioprotective effects [23]



apparently caused by a decrease in myocardial energy expenditures due to lower HR and cardiac diastole lengthening, especially at night, which is mentioned in other authors` works. For example, a study by Green EA et all revealed a negative chronotropic effect of melatonin two hours after its administration in patients with postural tachycardia syndrome [24].

Important melatonin clinical properties include its indirect lipid-correcting and hypoglycemic effect, proven antihypertensive action, as well as a beneficial influence on metabolic processes and weight normalization [15,18]. Melatonin has an exceptional antioxidant and absorption potential, both in extracellular and intracellular oxidative stress reduction [15,16] contributing to inhibition of lipoproteins atherogenic oxidation [25]. IHD patients are particularly prone to oxidative damage due to their reduced antioxidant protection [26]. Melatonin stabilizes the cell membrane and increases mitochondrial oxidative phosphorylation efficiency [27]. It also reduces electron leakage and free radicals generation [28]. Besides, the hormone has a powerful direct effect on peroxyl radicals removal, enhances various antioxidant enzymes activity and stimulates glutathione synthesis, thereby preventing its depletion [29]. This probably explains the melatonin therapy positive effect on IHD clinical course in patients of the 2nd group.

Melatonin modulates antioxidant defense that regulates Nrf2 pathways in peripheral blood mononuclear cells [30] and improves the expression level of CAT and MnSOD and NADPH oxidase (p22 and NOX2) [31].

Changes in the level of endogenous inflammatory markers in IHD patients can be related to day/night fluctuations in the circulating melatonin level [32], which has an anti-inflammatory effect and eliminates fibrosis formation. The hormone reduces the expression levels of inflammatory cytokines (TNF-α, IL-6 and COX-2) and fibrous markers (PC1 and TGF-β), binds NK-κB-DNA [33] and inhibits NF-κB activation by blocking IKK, JNK phosphorylation [16.34]. In this way it protects ventricular myocytes from ischemic reperfusion injury (IRI) of myocardium by inhibiting reactive oxygen species formation and Ca 2+ accumulation inside cells [16,31]. Probably, this unique cardioprotective melatonin property contributed to a beneficial effect on myocardium electrophysiological

activity in patients taking melatonin, which manifested itself in a significant decrease in the SVES and VES number.

It is worth noting that the nuclear melatonin receptor RORα is an endogenous IRI protective receptor and an important cardioprotection mediator [35]. In addition, the hormone suppresses the IRI caused ventricular arrhythmia and helps to reduce the post-infarction cardiosclerosis size [36].

Melatonin enhances nitric oxide (NO) bioavailability and provides cardiovascular protection by dilating blood vessels and lowering blood pressure [16,34], which is undoubtedly important for patients with coronary arteries atherosclerotic lesion. The NO formation enhances GABAergic inhibitory effects in the axons of neurons in the paraventricular nucleus [37]. They are preganglionic sympathetic neurons that control vascular tone, blood pressure and increase norepinephrine circulating concentration [38]. Thus, melatonin-dependent correction of circadian biorhythms and improvement in sleep quality characteristics can significantly weaken dominant sympathetic effects and change the course of the disease in elderly IHD patients. Thus, melatonin-dependent correction of circadian biorhythms and sleep quality improvement can significantly weaken the dominant sympathetic effect and change the disease course in elderly IHD patients.

5- Conclusion:

Timely correction of melatonin pathogenetic deficiency in elderly IHD patients with insomnia by including its pharmacological analogues in the treatment regimen manifests significant improvement in the patients` clinical condition. This is evidenced by the following: a decrease in anginal attacks frequency, dynamics in Holter ECG monitoring indicators and somnological characteristics.

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6- References

1. Atar D., Jukema J.W., Molemans B., Taub P.R., Goto S., Mach F., et all. New cardiovascular prevention guidelines: How to optimally manage dyslipidaemia and cardiovascular risk in 2021 in patients needing secondary prevention? *Atherosclerosis*, **319**, 51-61 (2021)
2. Shao C., Wang J., Tian J., Tang Y. Coronary Artery Disease: From Mechanism to Clinical Practice. *Advances in Experimental Medicine and Biology*, **1177**, 1-36 (2020)
3. Mortality according to Rosstat: official statistics. https://rosinfostat.ru/smertnost/#i-7. Accessed March 6th, 2020 (2020)
4. Zheng B., Yu C., Lv J., et al. Insomnia symptoms and risk of cardiovascular diseases among 0.5 million adults. *Neurology*, **93**(23), e2110-e2120 (2019)
5. Madsen M.T., Huang C., Zangger G., Zwisler A., Gögenur I. Sleep disturbances in patients with coronary heart disease: a systematic review. *J Clin Sleep Med*., **15**(3), 489-504 (2019)
6. Sands-Lincoln M., Loucks E.B., Lu B., et al. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the Women's Health Initiative. *J. Womens Health (Larchmt)*, **22**(6), 477-486 (2013)
7. von Känel, R., Princip, M., Schmid, JP. et al. Association of sleep problems with neuroendocrine hormones and coagulation factors in patients with acute myocardial infarction. *BMC Cardiovasc Disord*, **18**, 213 (2018).
8. Alshehri M.M., Alenazi A.M., Hoover J.C., Alothman S.A., Phadnis M.A., et all. A comparison of diabetes self-care behavior in people with type 2 diabetes with and without insomnia symptoms. *Acta Diabetol.*, **57**(6), 651-659 (2020)
9. Whitesell PL, Obi J, Tamanna NS, Sumner AE. A Review of the Literature Regarding Sleep and Cardiometabolic Disease in African Descent Populations. Front Endocrinol (Lausanne). 2018;9.
10. Kong A.S., Chan N.N., Chan J.C.N. The role of adipocytokines and neurohormonal dysregulation in metabolic syndrome. Curr. Diabetes Rev., 2(4), 397-407 (2006)
11. Riemann D., Baglioni C., Bassetti C., Bjorvatn B., Dolenc G., Ellis J.G., et all. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res.,* **26**(6), 675-700 (2017)
12. Crowley K. Sleep and sleep disorders in older adults. *Neuropsychol Rev*., **21**(1), 41-53 (2011)
13. Xie Z., Chen F., Li W.A., et al. A review of sleep disorders and melatonin. *Neurol Res*., **39**(6), 559-565 (2017)
14. Al-Wasidi A. S., Naglah A. M., Refat M., El-Megharbel S. M., Kalmouch A. et all. Synthesis, spectroscopic characterization and antimicrobial studies of Mn(II), Co(II), Ni(II), Cr(III) and Fe(III) Melatonin drug complexes. *Egyptian Journal of Chemistry*, **63**(4), 1469-1481 (2020).

15. Sun H., Huang Ff. & Qu, S. Melatonin: a potential intervention for hepatic steatosis. *Lipids Health Dis*, **14,** 75 (2015).
16. Alonso M., Collado P.S., González-Gallego J. Melatonin inhibits the expression of the inducible isoform of nitric oxide synthase and nuclear factor kappa B activation in rat skeletal muscle. *J Pineal Res*., **41**(1), 8-14 (2006)
17. Mohammadi S.M., Ghorbani M., Mazloom Z. Effects of melatonin supplementation on blood lipid concentrations: a systematic review and meta-analysis of randomized controlled trials. *Clinical Nutrition*, **37** (6), 1943-1954 (2018)
18. Imenshahidi, M., Karimi, G. & Hosseinzadeh, H. Effects of melatonin on cardiovascular risk factors and metabolic syndrome: a comprehensive review. *Naunyn-Schmiedeberg's Arch Pharmacol,* **393**, 521–536 (2020).
19. Wayne A M., Levin Y I. Principles of modern pharmacotherapy of insomnia. *Journal of Neurology and Psychiatry,* **5,** 39–43 (1998) [Вейн А. М., Левин Я. И. Принципы современной фармакотерапии инсомний. *Журнал неврологии и психиатрии, 5,* 39–43 (1998) (in Russia)]
20. Morin C.M., Belleville G., Bélanger L., Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*, **34**(5), 601-608 (2011)
21. Johns M.W. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*, **14**(6), 540-545 (1991)
22. Ozkalayci F., Kocabas U., Altun B. U., Pandi-Perumal S., Altun A. Relationship Between Melatonin and Cardiovascular Disease, *Cureus,* **13**(1), e12935 (2021)
23. Fu Z., Jiao Y., Wang J., Zhang Y., Shen M., Reiter R.J., Xi Q. and Chen Y. Cardioprotective Role of Melatonin in Acute Myocardial Infarction. *Front. Physiol.*, **11**, 366 (2020)
24. Simko F., Baka T., Paulis L., Reiter R.J. Elevated heart rate and nondipping heart rate as potential targets for melatonin: a review. *Journal of Pineal Research*., **61**(2), 127-137 (2016)
25. Albrecht M., Zitta K., Groenendaal F., van Bel F., Peeters-Scholte C. Neuroprotective strategies following perinatal hypoxia-ischemia: Taking aim at NOS. *Free Radical Biology and Medicine*, **142**, 123-131 (2019)
26. Jyrkkänen H-K., Kansanen E., Inkala M., et al. Nrf2 regulates antioxidant gene expression evoked by oxidized phospholipids in endothelial cells and murine arteries in vivo. *Circ Res*., **103**(1), e1-9 (2008)
27. Mohamed E. E., Abdelmoeti N. M.; Mohamed S. G. Adjuvent effect of Melatonin premedication on propofol induction dose. *Egyptian Journal of Chemistry*, **64** (1), 431 - 436 (2021)
28. Tordjman S., Chokron S., Delorme R., Charrier A., Bellissant E., Jaafari N., Fougerou C. Melatonin: Pharmacology, functions and therapeutic benefits. *Current Neuropharmacology*, **15**(3), 434-443 (2017)
29. Bhattacharya S., Patel K.K., Dehari D., Agrawal A.K., Singh S. Melatonin and its ubiquitous anticancer effects. *Mol Cell Biochem,* **462**(1-2), 133-155 (2019)
30. Haghjooy J.S., Ziaei A., Ziaei S., Ziaei E., Mirmohammad-Sadeghi M. The Effect of Preoperative Melatonin on Nuclear Erythroid 2-Related Factor 2 Activation in Patients Undergoing Coronary Artery Bypass Grafting Surgery. *Oxidative Medicine and Cellular Longevity,* **2013**, Article ID 676829, 6 pages, (2013)
31. Yeung H-M., Hung M-W., Lau C-F., Fung M-L. Cardioprotective effects of melatonin against myocardial injuries induced by chronic intermittent hypoxia in rats. *J Pineal Res*., **58**(1), 12-25 (2015)
32. Dominguez-Rodriguez A., Abreu-Gonzalez P., Garcia M., et al. Light/dark patterns of interleukin-6 in relation to the pineal hormone melatonin in patients with acute myocardial infarction. *Cytokine*, **26**(2), 89-93 (2004)
33. Qin W., Li J., Zhu R., Gao S., Fan J., Xia M., Zhao R.C., Zhang J. Melatonin protects blood-brain barrier integrity and permeability by inhibiting matrix metalloproteinase-9 via the NOTCH3/NF-kappaB pathway. *Aging,* **11**(23), 11391-11415 (2019)
34. Alsayed M., El-Kady D. S., Tantawy M. A., Abdelhalim M. M., Elazabawy S. R., Abdallah A. E. M., Elmegeed G. A. Novel Melatonin derivatives: synthesis, anticancer evaluations and molecular-docking study. *Egyptian Journal of Chemistry,* **64** (3), 1517 - 1533 (2021)
35. He B., Zhao Y., Xu L., et al. The nuclear melatonin receptor RORα is a novel endogenous defender against myocardial ischemia/reperfusion injury. *J. Pineal Res*., **60**(3), 313-326 (2016)
36. Zhang Y., Wang Y., Xu J., Tian F., Hu S., Chen Y. Melatonin attenuates myocardial ischemia-reperfusion injury via improving mitochondrial fusion/mitophagy and activating

the AMPK-OPA1 signaling pathways. *J. Pineal Res*., **66**(2), e12542 (2019)
37. Rosi S., Giovannini M.G., Lestage P.J., Muñoz C., Corte L.D., Pepeu G. S 18986, a positive modulator of AMPA receptors with cognition-enhancing properties, increases ACh release in the hippocampus of young and aged rat. *Neuroscience Letters*, **361**(1-3), 120-123 (2004)
38. Dagnino-Subiabre A., Orellana J.A., Carmona-Fontaine C., et al. Chronic stress decreases the expression of sympathetic markers in the pineal gland and increases plasma melatonin concentration in rats. *Journal of Neurochemistry,* **97**(5), 1279-1287 (2006)