Alkaloids of Peganum harmala L. and their Pharmacological Activity

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Abstract

BACKGROUND: Peganum harmala L. contains 17 quinazoline and indole structural alkaloids. Harmaline, harmine, harmalol, and L-peganin (vasicine) are pharmacologically active. It was established that in alkaloids contained in the seeds, 50–95% falls on harmaline that harmine is dominated in roots (67–74% of the total of extractive substances), and in the aerial part, the main mass is peganin (up to 76% of the total alkaloids). Beta-carboline alkaloids of P. harmala L. inhibit monoamine oxidase, thereby exerting a neuroprotective effect.

AIM: The study of the pharmacological properties of harmine hydrochloride.

MATERIALS AND METHODS: The neurotropic activity of harmine hydrochloride was studied in the Porsolt’s and “elevated plus maze” tests, as well as in experimental models of haloperidol catalepsy, hypobaric hypoxia, and normobaric hypoxia.

RESULTS: In the study of acute and chronic toxicity, it was determined that harmine hydrochloride belongs to the category of moderately toxic substances (hazard Class II). Based on the results of molecular docking, the presence of strong bonds in harmine hydrochloride with the serotonin 5-HT2 receptor, dopamine D2 receptor, as well as monoamine oxidase A and B was revealed, which indicates the implementation of the mechanism of neurotropic action of harmine hydrochloride at the level of synaptic neurotransmission of monoamines (dopamine, serotonin, and others). It was established that harmine hydrochloride has antihypoxic activity in the hypobaric hypoxia test and exhibits pronounced antidepressant activity in the Porsolt’s test. In the course of the study of pharmacokinetics and bioavailability, it was revealed that with the administration of harmine hydrochloride, the quantitative content is quickly achieved and the concentration of the active substance in the blood significantly increases. The relative bioavailability of harmine hydrochloride is 112.7%.

CONCLUSIONS: The presented data of preclinical studies showed that harmine hydrochloride has antidepressant, antihypoxic, and antiparkinsonian effects, eliminates catalepsy caused by haloperidol in rats, and reduces oligokinesia and rigidity in the parkinsonian syndrome test. In terms of antiparkinsonian effect, harmine hydrochloride is not inferior to amitriptyline. The study of the relative bioavailability of harmine hydrochloride in experimental animals showed that harmine hydrochloride is absorbed much faster when administered orally, quickly reaching the highest concentration in blood plasma. Based on the results of molecular docking, the presence of strong bonds in harmine hydrochloride with monoamine oxidases A and B was revealed, which indicates the implementation of the mechanism of the antidepressant action of the alkaloid at the level of synaptic neurotransmission.

Introduction

Peganum harmala L. (P. harmala L. – Figure 1) is a perennial herb of the Zygophyllaceae family, widespread in Central Asia, North Africa, and the Central East [1], [2] (Figure 1). This type of plant is found everywhere in Kazakhstan, excluding the highlands. During our expeditionary research, commercial stocks of P. harmala L. were revealed [3]. According to the results of the route reconnaissance survey of the Kurbai mountain range of the Zhambyl region, the Ordabasy district of the Turkestan region, and the Zhanakorgan district of the Kyzylorda region, the distribution and reserves of raw materials of P. harmala L. were determined. On the territory of Ordabasynsky district north-west of the Zhambyl village, operational reserves of 18.6 tons in the calculation of dry raw materials and the volume of annual procurement of not more than 6.2 tons of dry raw materials were revealed. South-east of the Koltagan village, near the Bergen Isakanov village, operational stock is 13.5 tons with annual procurement volume of no more than 4.5 tons of dry raw materials. Herbarium specimens are kept in the collections of JSC “International Research and Production Holding Phytochemistry.”

P. harmala L. has been used for a long time in traditional medicine in Turkey, Iran, and China for the treatment of hypertension, lumbago, asthma, diabetes, various infections, and also as an antitumor, anti-inflammatory, and anti-inflammatory agent [4], [5]. In the Caucasus, it is sometimes used as a sleeping pill, like Indian hemp. In Azerbaijan, P. harmala L. is universally known as a medicinal plant.

In Tajikistan, paralytics are fumigated with this plant, and poultices for tumors are made from the leaves. Decoction of seeds together with flax or...
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L., the content of alkaloids P. harmala 0.027%), and deoxyvazicinone 1.23%), were 0.017%), along with harmine 0.012%), deoxypeganin 0.04%), and harmalin 0.015%). In P. harmala L. and its extracts of uses as a sedative and anti-inflammatory. Experimental results indicate that extracts of P. harmala L. are inhibitors of cholinesterase and monoamine oxidase and have antitumor, anticoagulant, hypotensive, anti-diabetic, antibacterial, antiviral, anti-inflammatory, and antiparasitic activities. Seeds exhibit hypnotic, antiplasmodic, cytotoxic, and vasorelaxant activities [6], [7]. As a result of pharmacological studies in recent years, antitumor, insecticidal, hypoglycemic, anti-diabetic, hepatoprotective, analgesic, antibacterial, and fungicidal actions of individual organs of P. harmala L. and its extracts have been revealed [8], [9], [10], [11], [12] (Figure 2).

Fig 1: P. harmala L. and its alkaloid containing organs

Figure 2: Alkaloids of P. harmala L. and their pharmacological actions

In P. harmala L., the content of alkaloids varies according to the plant’s organs. The aerial part contains 0.69%, end of the growing season, in the aerial part is 2–2.3%; during the flowering period in the aerial part – 2.17%, in young roots – 3.32%, in old roots – 1.68%; during budding in the aerial part – 2–2.3%; during the flowering period in the aerial part – 1.86–1.95%; the beginning of fruiting – 1.3%; mass fruiting – 0.69%; end of the growing season, in the aerial part – 0.5%, in the roots – 1.8%, and seeds – 5%. All parts of P. harmala L. contain alkaloids, seeds, and roots are especially rich in them, and more than a quarter of them are harmine 1. The seeds of P. harmala L. also contain harmaline 2. It usually accounts for half to two-thirds of alkaloids in total. The roots contain only harmine 1; in flowers and stems – peganin 3; there was also found harmalol 4 and a number of other alkaloids.

Harmine 1 is found in plants P. harmala L. and Banisteia varieties, namely, Banisteia caapi L., Spruce, Banisteia lutea L., and Banisteia metallicolor L. Harmine 1 was first isolated in the 19th century from the seeds of P. harmala L. and Banisteriopsis caapi M., which are traditionally used in the Middle East, Central Asia, and the South of America [13], [14], [15].

Harmine hydrochloride 5 has a therapeutic effect in Parkinsonism after lethargic encephalitis and tremors. Peganin hydrochloride 6 is approved as an anticholinesterase agent [16].

Fig 2: Alkaloids of P. harmala L. and their pharmacological actions

Alkaloids of P. harmala L. and their Pharmacological Activity

Alkaloids, flavonoids, steroids, amino acids, anthraquinones and polysaccharides, and volatile oils were isolated from P. harmala L. and studied [17], [18], [19]. Among these compounds, alkaloids were the main components, the total content of which was 2–5%. Alkaloids were found in the roots (up to 2% by weight) and seeds (4.3–5.6% by weight) of the plant [20].

The pharmacologically active constituents of P. harmala L. are alkaloids, found mainly in seeds and roots. At the same time, harmine 1, harmaline 2, harmalin 4, tetrahydroharmine 7, harmalicin 8, 3,4-dihydroharmane 9 and 7-hydroxy-3,4-dihydro-norharm-1-one 10, as well as tetracyclic lactams – harmalanine 11 and harmalacin 12 [14], [21], [22], β-carboline alkaloids were isolated from P. harmala L. and their structures were established.

Julius Fritzsche was the first to isolate a new alkaloid from P. harmala L. seed husks in 1848 and named harmine 1. A related harmaline was isolated from P. harmala L. and named by Friedemann Gebel in 1837. The pharmacology of harmine 1 was not studied in detail until 1895. Harmine 1 and harmaline 2 structures were established in 1927 by Hellmuth et al. [23].

The quinazoline alkaloids of P. harmala L. can be divided into two groups: Derivatives of 3,4-dihydroquinazoline (peganin 3, deoxypeganin 13, peganol 14, peganidine 15, and 4-(3-H)-quinazolinone (vazicinone 16, deoxyvazicinone 17, and peganin 18). Peganin 3 (0.04%), deoxypeganin 13 (0.012%), vazicinone 16 (0.027%), and deoxyvazicinone 17 (0.017%), along with harmine 1 (1.23%), were isolated by us from P. harmala L. collected in Kurday district of Zhambyl region [24].

The pharmacological action of P. harmala L. is associated with the presence in its composition of β-carboline alkaloids – harmine 1 and its analogs (Figure 2) [25], [26], [27]. The alkaloids of P. harmala L. exert psychoactive effect.

Harmine 1 is a hallucinogen, a stimulant of the central nervous system, a short-term inhibitor of
monoamine oxidase. In Germany, since 1927, the drug “Harmine,” developed by Merck Company, has been actively used for the treatment of patients with post-encephalitic Parkinsonism and tremor paralysis. However, by the end of 1929, doctors realized the unrealistic expectations of the drug “Harmine” and emphasized in their presentations that the pharmacological effects of harmine were variable and shortlived [28]. At present, harmine was excluded from the nomenclature of drugs due to the appearance of more effective and safe MAO inhibitors [29].

Harmaline 2 acts as an acetylcholinesterase inhibitor and also stimulates the release of dopamine in the corpus striatum in rats at very high doses. Since harmaline is a reversible inhibitor of monoamine oxidase A, theoretically it can cause both serotonin syndrome and hypertensive crisis in combination with tyramine, serotonergic, catecholaminergic drugs, or prodrugs. Harmaline 2 enhances the anabolic metabolism of serotonin to N-acetylserotonin (melatonin) and then to melatonin, the main sleep-regulating hormone and a powerful antioxidant [30], [31].

A study [32] reports on the antiviral activity of harmaline 2 against herpes 1 and 2 (HSV-1 and HSV-2) by inhibiting early transcription of the virus at a non-cytotoxic concentration.

It is known that harmaline 2 acts as an inhibitor of histamine-N-methyltransferase. This explains how harmaline 2 has a stimulating effect on wakefulness.

Deoxypeganin 13 and peganin 3 are used as anticholinesterase drugs [30]. On the basis of deoxypeganin, the drug “Deoxypeganin hydrochloride” was created, which is used to treat lesions of the peripheral nervous system, Parkinson’s disease, and the consequences of cerebrovascular accident. The drug helps to restore neuromuscular conduction, increases the tone of unstriated muscles.
Peganin hydrochloride is approved as an anticholinesterase agent for myopia and myasthenia, and also as a laxative for constipation and intestinal atony of various origins. Harmine, contained in the seeds of P. harmala L., is recommended in the treatment of the consequences of epidemic encephalitis, tremor palsy and Parkinson's disease.

On the other hand, harmine and its derivatives are considered as promising sources of neurotropic drugs. Harmine has antidepressant, anxiolytic, behavioral, and antitumor potential, both in vitro and in vivo, and can also be used to treat the effects of epidemic encephalitis and Parkinson's disease [33].

Beta-carboline alkaloids exhibit a wide range of psychopharmacological effects by interacting with benzodiazepine, imidazoline, serotonin, and opiate receptors, as well as by inhibiting monoamine oxidase [34]. Neurochemical and behavioral studies have shown that beta-carboline alkaloids, harmine 1 and its derivatives, facilitate dopaminergic transmission and interact with dopaminergic D1 and D2 receptors in the corpus striatum [35]. It is known that the majority of beta-carboline alkaloids are potent inhibitors that metabolize the neurotransmitters of catechol-amines [36]. Several potential molecular targets that were identified for the central pharmacological effects of harmine include zinc-dependent CDK kinases (CDK1, 2, and 5), Dyrk, MAO-A, 5-HT2A sites, and imidazoline receptors [37]. This alkaloid has antidepressant activity by interacting with MAO-A and several cell surface receptors, including the serotonin receptor 2A (5-hydroxytryptamine receptor 2A, 5-HT2A), have the ability to stimulate the release of dopamine, justifying its use in the treatment of brain disorders [38].

In addition, it was reported that harmine exhibits cytotoxic activity in relation to human tumor cell lines [39].

During the study of cytotoxic and genotoxic effects of harmine on fibroblasts of the lung of the Chinese hamster V79 in vitro using single-stranded gel analysis, it was determined that at a dose of 40–50 μg/ml, this alkaloid increases the frequency of aberrant cells and induces DNA damage [40]. Other authors confirmed its ability to induce single or double DNA breaks. The cytotoxicity of harmine was established on a shrimp lethality test and by microdilution to determine the minimum inhibitory concentration [42]. This indole alkaloid activates both internal and external pathways of apoptosis and regulates several transcription factors and pro-inflammatory cytokines, and reduces tumor capillary formation, showing an angiogenic inhibitory potential [43], [44]. It also inhibits the breast cancer resistance protein, which overexpresses MDA-MB-231 breast cancer cells [45]. Harmine toxicity was assessed by cytochalasin-B-blocked micronucleus assay and viability of colony assay with four different human cells, including non-transformed CCD18Lu and transformed HeLa, C33A, and SW480 cells [39]. Harmine showed an inhibitory effect on cell proliferation against all human carcinoma cells, while in cytotoxicity assays, it showed a strong inhibitory effect on the growth and proliferation of carcinoma cells, while it did not significantly affect resting fibroblasts [46]. In other studies, harmine has shown cytotoxicity against HL60 and K562 cell lines [47].

This indole alkaloid is a potent inhibitor of kinase 1A (Dyrk1A) involved in Down's syndrome and functions as an ATP-competitive inhibitor against Dyrk1A [48].

The results of a study of the comparative effectiveness of anti-venom for various psychoactive drugs indicated that harmine is predominantly effective against various addictive substances (coca > amphetamines > nicotine) [49].

This alkaloid significantly increases the expression of the GLT-1 protein and significantly attenuates the expression levels of interleukin-1β and tumor-α necrosis factor, thereby weakening the apoptotic death of neurons in the hippocampus [50].

Rodent studies have shown that harmine may also reduce brain infarction volume and neuronal cell death due to the activation of the glutamate transporter, which reduces excessive and neurotoxic glutamate levels, suggesting that harmine may also have neuroprotective properties. This alkaloid is a selective inhibitor of the protein kinase Dyrk1A, a molecule essential for the development of the nervous system, and supports the survival of dopaminergic neurons in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Parkinson's disease) [51], [52].

Harmine interacts with the serotonin 2A receptor and was shown to have an antidepressant effect in rodent models [53]. In addition, it increases brain-derived neurotrophic factor (BDNF) in the rat hippocampus. In humans, decreased BDNF levels are associated with major depression. In addition, MAO-A inhibitors reduce the breakdown of serotonin and norepinephrine and are used to treat depression [54].

Despite considerable evidence for antidepressant effects in animal models, harmine has never been used as an antidepressant in humans. However, it was already mentioned in 1930 that it may be useful for patients with cataton schizophrenia, and has recently been again suggested as a potential treatment option for psychosis.

Beta-carboline alkaloids inhibit monoamine oxidase, thereby exerting an antidepressant effect. Therefore, harmine has neuroprotective activity, reduces oxidative stress in nervous tissue, increases BDNF, improves cognitive functions, and increases memory capacity [54].

Thus, harmine has a neuroprotective effect, which is associated with the interaction of this alkaloid with serotonin and dopaminergic receptors D1 and D2.
inhibition of monoamine oxidase. It shows cytotoxic activity against human tumor cells, while causing DNA break.

Considering that harmine 1 exhibits hallucinogenic and toxic properties in high doses, which are much higher than the usual clinical doses, we carried out a study of acute and chronic toxicity, determination of antidepressant, antiparkinsonian, antihypoxic, and anxiolytic activity, a study of the pharmacokinetics and bioavailability of harmine hydrochloride 5 in small doses, and molecular docking on biological targets.

Pharmacological Study of Harmine Hydrochloride

Acute and chronic toxicity

According to the results of the study of acute toxicity, it was established that harmine hydrochloride 5 belongs to the category of moderately toxic substances. LD₅₀ of harmine hydrochloride 5 when administered intraperitoneally to laboratory rats is 87 mg/kg. According to the classification of GOST 12.1.007-76, harmine hydrochloride when administered intragastrically to rats is moderately toxic (hazard Class II). Approximately, the same results were obtained in South America in the study of harmine 1, derived from the Ayahuasca plant, in the form of a slight decrease in the viability of the cell culture treated with a solution concentration of 10.5 μg/ml for 48 h, but even showed some increase in the proliferation of nerve cells under in vitro exposure to primary alkaloids. According to the results of a study of chronic toxicity, harmine hydrochloride 5 showed that its administration in doses of 2.5 mg/kg, 5 mg/kg, 9 mg/kg, and 10 mg/kg to laboratory rats for 3 months did not cause pathological changes in the general condition of the animals. Minor deviations in the functional state of internal organs and blood biochemical parameters were noted. It was established that harmine hydrochloride 5 does not have an allergenic, carcinogenic, and mutagenic effect, does not have immunotoxicity and reproductive toxicity.

Study of the Pharmacokinetics of Harmine Hydrochloride

In experiments on male Wistar rats (n = 180) using an Agilent 1260 high-performance liquid chromatography and an Agilent 6120 mass spectrometer, it was established that the time of the main elimination from the body after a single oral administration of harmine hydrochloride 5 does not exceed 24 h. The residual concentration of the substance during this registration period was 3.11 ± 1.3 ng/mL for a dose of 4.5 mg/kg and 10.30 ± 1.13 ng/ml – 40 mg/kg. The semiejection period of harmine hydrochloride 5 in the urine at a dose of 40 mg/kg was 3.00 ± 0.8 h, at a dose of 4.5 mg/kg – 2.00 ± 0.6 h. The half-life of harmine hydrochloride 5 from the blood was 5.00 ± 1 h (40 mg/kg) and 4.00 ± 0.1 h (4.5 mg/kg). In blood serum, the clearance of harmine hydrochloride 5 at a dose of 40 mg/kg was 63.40 ± 15.9 l/h, at a dose of 4.5 mg/kg – 54.40 ± 13.6 l/h. With the administration of harmine hydrochloride 5, the quantitative content is quickly achieved and the concentration of the active substance in the blood significantly increases.

Bioavailability

The relative bioavailability of harmine hydrochloride 5 was studied at a dose of 50 mg in 12 lagomorph male chinchilla rabbits. It was established that harmine hydrochloride 5 has pharmacokinetic advantages, namely, a relatively rapid achievement of the maximum plasma concentration (T_max) and a significant increase in the concentration of the active substance in the blood, and at the same time, it was absorbed much faster when administered orally (per os). The relative bioavailability of harmine hydrochloride 5 is 112.7%.

Antidepressant Activity

The antidepressant activity of harmine hydrochloride 5 was studied in vivo in the Porsolt's test (behavioral despair).

The stress state was induced in mice by forced swimming. The animals were placed in a cylinder 10 cm in diameter and 25 cm in height. The cylinder was filled 1/3 with water (27°C). After unsuccessful attempts to get out of the water, the animals assumed a characteristic motionless posture, which was regarded as the appearance of depression (despair). All active attempts of animals to get out of the water were recorded during the first 6 min after immersion into water. Behavioral indicators were as follows: The duration of the first act of motor activity, the time of active swimming, and the time of immobilization. The test subjects at a dose of 10 mg/kg were administered orally as a suspension in 1% starch mucilage intragastrically 1 h before the study. Control animals received an equal volume of starch mucilage. Reference drug “ Amitriptyline” at a dose of 10 mg/kg was administered orally as a suspension in
It was established that in the Porsolt's test, harmine hydrochloride \(5\) exhibited a pronounced antidepressant effect. Hence, under the action of harmine hydrochloride \(5\) at a dose of \(10\) mg/kg, a significant increase in the duration of active swimming was observed by 1.2 times, and there was also a decrease in the immobilization time by 2.1 times, compared with the control group.

### Antiparkinsonian Activity

The antiparkinsonian activity of harmine hydrochloride \(5\) was determined in models of haloperidol catalepsy and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonian syndrome in mice compared with levodopa, a reference antiparkinsonian drug, and placebo-control. In the haloperidol catalepsy model, harmine hydrochloride \(5\) at a dose of 2.5 mg/kg showed an efficacy comparable to levodopa at a dose of 50 mg/kg and a 3-fold decrease in the level of catalepsy in the “Stride Length Test,” “vertical pole,” and “rotating pole” tests.

On the model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism, the assessment of rigidity by change in stride length showed results in the groups of harmine hydrochloride \(5\) at a dose of 2.5 mg/kg and levodopa 50 mg/kg, comparable to the intact group and superior to the control group without therapy. The assessment of oligokinesia in the open field test in the groups of harmine hydrochloride \(5\) and levodopa gave comparable results. Motor deficit in the “vertical pole” test in the early stages regressed in the group receiving harmine hydrochloride \(5\) at a dose of 5 mg/kg and was comparable to the group receiving levodopa at a dose of 100 mg/kg. Evaluation of movements coordination in the “rotating pole” test in the groups of harmine hydrochloride \(5\) and levodopa showed a result that exceeded the control group by 2.1 times with the preliminary administration of harmine hydrochloride \(5\) at a dose of 5 mg/kg and levodopa 50 mg/kg, comparable to each other. In the study, an antiparkinsonian effect of harmine hydrochloride \(5\) was confirmed, comparable to levodopa based on the results of assessing the severity of rigidity, oligokinesia, motor, and coordination disorders. Comparative analysis of the data obtained in the experiment on C57Bl/6 mice in three doses (2.5, 5.0, and 10.0 mg/kg), ranging from 0.1 to 0.001 \(\text{LD}_{50}\), on the effects of acute and subchronic systemic administration of harmine hydrochloride \(5\), made it possible to confirm the presence of psychotropic effects of the activating type of harmine hydrochloride.

### Antihypoxic Activity

The antihypoxic effect of harmine hydrochloride \(5\) was studied in hypobaric hypoxia and normobaric hypoxia with hypercapnia in a hermetic volume on outbred male rats. The model of hypoxia with hypercapnia in the hermetic volume was carried out according to the standard protocol [55]. The mice were placed in a sealed 190 ml glass container. The lifespan of the animals was assessed in relation to the control. The difference in the weight of the animals did not exceed 2–3 g.

Harmine hydrochloride \(5\) at a dose of 2.5 mg/kg and at a dose of 5 mg/kg increased the lifespan of animals by 2.48 and 2.4 times, respectively, relative to the reference drug “Mexidol.” Under the influence of harmine hydrochloride \(5\), the number of animals also increased, the latent time of death of which was 2 or more times higher than the latent time of death in the corresponding control (equal to an average of 100 s). The revealed antihypoxic effect of harmine hydrochloride \(5\) in small doses is comparable to the effect of “Mexidol” at a dose of 100 mg/kg and exceeded the activity of “Mexidol” when used at a dose of 200 mg/kg. Harmine hydrochloride \(5\) at doses of 2.5 mg/kg and 5 mg/kg has antihypoxic activity in the test of hypobaric hypoxia, comparable to the activity of “Mexidol” at a dose of 100 mg/kg.

### Anxiolytic (anti-anxiety) Action

The anxiolytic activity of harmine hydrochloride \(5\) was studied in the “elevated plus maze” test. The method of studying anxiolytic activity in the “elevated plus maze” test is based on the natural preference of dark holes by rodents, as well as on the fear of being in open areas and falling from a height. The animals were placed in an elevated plus maze and the following indicators of anxiolytic activity were recorded for 3 min: Latent time of exit into the open sleeve (s), the number of exits into the open sleeve, and the total time spent in the open sleeves of the maze (s).

One of the most significant evaluation criteria in the study of anxiolytic activity in the elevated plus maze was the time spent by animals in the open sleeve, which indicates the presence or absence of natural
phobias, open and illuminated spaces in laboratory animals.

With the administration of harmine hydrochloride 5, the manifestation of anxiety in animals decreased. Hence, the time spent by animals in open sleeves in the group with the use of harmine hydrochloride 5 was 18.8±8.5 s and exceeded the showings of group of reference drug amitriptyline (5.5±6.0 s). The number of entries into the open sleeves in the harmine hydrochloride 5 group was comparable to the comparison group – amitriptyline.

The showings of the number of overhangs in the group with the administration of harmine hydrochloride 5 were higher than the control group and are comparable with the data of the comparison group. The number of standings in animals in the group with harmine hydrochloride 5 was the same as in the comparison group (Table 2).

| Group                     | Time spent in a closed sleeve, (sec) | Time spent in the open sleeve, (sec) | Number of entries into open sleeves, (times) | Number of entries into closed sleeves, (times) | Number of hangings, (times) |
|---------------------------|--------------------------------------|--------------------------------------|---------------------------------------------|------------------------------------------------|-----------------------------|
| Intact rats               | 113.8 ± 23.9                         | 9.7 ± 16.0                           | 0.8 ± 0.4                                   | 4.0 ± 2.4                                      | 3.8 ± 4.7                   |
| Control (without treatment)| 131.2 ± 35.3                         | 8.0 ± 9.8                            | 0.5 ± 0.5                                   | 4.2 ± 1.7                                      | 5.0 ± 1.6                   |
| Reference group           | 133.8 ± 16.9                         | 16.0 ± 4.5                           | 0.8 ± 1.0                                   | 3.8 ± 1.5                                      | 2.8 ± 1.2                   |
| Amitriptyline – 10 mg/kg  | 120.0 ± 18.5                         | 18.8 ± 8.5                           | 1.3 ± 0.5                                   | 2.2 ± 0.4*                                     | 10.0 ± 2.3*                 |
| Harmine hydrochloride 5   | 120.0 ± 18.5                         | 18.8 ± 8.5                           | 1.3 ± 0.5                                   | 2.2 ± 0.4*                                     | 10.0 ± 2.3*                 |

*р < 0.05 compared with the values in animals of the control group.

Thus, harmine hydrochloride 5 reduced feelings of fear and anxiety in animals, not inferior in the level of manifestation of anti-anxiety action to the reference drug amitriptyline.

**Molecular Docking of Harmine Hydrochloride**

Molecular docking of harmine hydrochloride 5 was carried out on biological targets: Serotonin 5-HT<sub>2C</sub> receptor, dopamine D<sub>2</sub> receptor, and monoamine oxidase using the Maestro graphical interface of the Schrödinger Suite software package (Schrödinger, LLC, New York, NY, 2017). The docking mode was SP (standard precision). As the final results, we used the value of the scoring function G-Score, which shows the energy and strength of binding of the ligand to the target molecule (Table 3).

| Compound | Serotonin 5-HT<sub>2C</sub> receptor | Dopamine D<sub>2</sub> receptor | Monoamine oxidase A (MAO-A) | Monoamine oxidase B (MAO-B) |
|----------|-------------------------------------|---------------------------------|-----------------------------|----------------------------|
| Harmine hydrochloride 5 | 6.199 | −5.306 | −7.503 | −7.145 |

As a result of the molecular docking of harmine hydrochloride 5, it showed the best binding energies with monoamine oxidases A and B (−7.503 and −7.145 kcal/mol, respectively). Harmine hydrochloride 5 showed a relatively strong bond with the serotonin 5-HT<sub>2C</sub> receptor and the dopamine D<sub>2</sub> receptor (−6.199 and −5.366 kcal/mol, respectively) (Figures 3-6).
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Conclusions

The alkaloids of P. harmala L. are potential sources of original drugs. First of all, beta-carboline alkaloids have neurtropic activity, since they interact with monoamine oxidase A and serotonin 2A receptor (5-hydroxytritamine receptor 2A, 5-HT₂A) and dopamine D₂ receptor. Among them, harmine 1 is especially distinguished by its neurtropic action.

The data of preclinical studies presented by us showed that harmine hydrochloride 5 has antidepressant, antihyposic, and antiparkinsonian effects, eliminates catalepsy caused by haloperidol in rats, and reduces oligokinesia and rigidity in the parkinsonian syndrome test.

In terms of antiparkinsonian effect, harmine hydrochloride 5 is not inferior to amitriptyline. The study of the relative bioavailability of harmine hydrochloride 5 in experimental animals showed that harmine hydrochloride 5 is absorbed much faster when administered orally, quickly reaching the highest concentration in blood plasma. At the same time, it reduces the level of cortisol in the experiment of stress-induced disorder.

And also as a result of chronic toxicity, it was established that harmine hydrochloride 5 does not have an allergenic, carcinogenic, and mutagenic effect, and does not have immunotoxicity and reproductive toxicity.

Thus, on the basis of the studies carried out, harmine hydrochloride 5 should be considered as a potential substance for the development of an original neurtropic drug.

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