PREVENTIVE EFFECT OF N-STEARYLETHANOLAMINE ON MEMORY DISORDERS, BLOOD AND BRAIN BIOCHEMICAL PARAMETERS IN RATS WITH EXPERIMENTAL SCOPOLAMINE-INDUCED COGNITIVE IMPAIRMENT

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The impairment of cognitive functions is the most studied medical and social problem nowadays. The aim of this study was to evaluate the protective effects of N-stearoyl ethanolamine (NSE) on memory state, blood and brain biochemical parameters in rats under scopolamine-induced cognitive impairment. The results of this study shown that NSE administration to rats per os (5 mg/kg, 5 days, during last 3 days NSE was administrated 20 min prior to scopolamine injection (1 mg/kg, once daily for 3 days, intraperitoneally)) prevented the development of memory impairment. In particular, NSE action was associated with the prevention of increase in acetylcholinesterase activity, changes in phospholipid, free and esterified cholesterol level in hippocampus and frontal cortex, and disruption in pro-/antioxidant balance in blood and studied brain sections. Considering the above mentioned biological effects, NSE is a promising drug candidate for integrative therapy of cognitive impairment of different profiles.

Keywords: N-stearoyl ethanolamine, phospholipids, cholesterol, superoxide dismutase, catalase, glutathione peroxidase, nitrotyrosine, TBARS, acetylcholinesterase, scopolamine.

It is known that the endocannabinoid system plays an important role in the regulation of memory, learning processes and emotional behaviour [1]. Inhibition of endocannabinoid hydrolysis contributes to the protection of blood-brain barrier integrity and prevents the development of neurological and behavioral disorders in rats [2]. Previous studies with fatty acid amidohydrolase (FAAH) inhibitors showed the increase of memory capacity and learning ability, contributing to the formation of a memorable trace via activation of PPARα and CB1 receptors [3]. It was found that saturated N-acyl ethanolamines (NAEs) modulate the activity and expression of FAAH [4], and as a high affinity ligands of PPARα receptor [5], take part in memory formation processes. The results of previous studies in mice revealed the protective effect of N-stearoyl ethanolamine (NSE) on brain function, followed by the improvement of memory capacity in animals treated with lipopolysaccharide or immunized with the extracellular domain of the α7 nicotinic acetylcholine receptor [6]. In addition, NSE exhibited cannabimimetic activity [7], however, this effect was not mediated by the activation of CB receptors. It has been shown by earlier studies that NSE may prevent pathological changes in tissues via different biochemical mechanisms under multiple pathologies conditions [6]. Therefore, considering the already known biological effects of NSE, it was interesting to study its effects on memory state, blood and brain biochemical parameters in rats with experimental scopolamine-induced cognitive impairment.
Materials and Methods

The study was conducted on 24-month-old Sprague-Dawley outbred rats weighing between 350–400 g. These animals are considered aged. Rats were housed in standard cages with free access to food and water. All animal procedures were conducted in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes (Strasbourg, 1986).

To simulate cognitive pathology in animals we used scopolamine, a muscarinic antagonist which exhibits m-cholinoreceptor blocking activity and is employed as the gold standard for inducing memory impairments in experimental models [8].

Animals were divided into three experimental groups with 7 rats in each: “Control”, “Scopolamine” – rats were injected intraperitoneally with scopolamine (1 mg/kg, once daily for 3 days) to simulate cholinergic deficiency, “NSE + Scopolamine” – rats were orally received the water suspension of NSE (5 mg/kg, 5 days: during last 3 days NSE was administrated 20 min prior to scopolamine injection, per os) and were injected intraperitoneally with scopolamine (1 mg/kg, once daily for 3 days).

The effect of NSE on memory of rats was studied using the passive avoidance reflex (PAR) test. The percentage of animals in the group with preserved passive avoidance reflex was evaluated in this test. PAR was trained, using a common technique of experimental light-dark chamber with an aperture, 15 min after the last administration of scopolamine [9, 10]. PAR retention was checked after 24 h. Rats that did not enter the dark chamber for 3 min were considered to pass the learning criteria. After 60 min of testing, animals were euthanized under CO2 anesthesia. Whole blood samples and separated brain structures were collected for biochemical studies.

The lipid extraction by Bligh and Dyer method [11] was performed to estimate lipid composition of hippocampus and frontal cortex. After that lipid extracts were separated by thin-layer chromatography, using solvent systems for the first dimension chloroform (65): methanol (30): ammonia (6): benzene (10), and the second dimension chloroform (5): methanol (1): acetic acid (1): water (0.5): acetone (2) [12]. The level of individual phospholipids was determined by Vaskovskiy and Kostetskiy method [13].

The intensity of the lipid peroxidation processes was carried out by the thiobarbituric acid reactive substances (TBARS) assay [14], superoxide dismutase activity (SOD, EC 1.15.1.1) was determined by the level of nitro blue tetrazolium reduction in the presence of NADH and phenazine methosulfate [15], catalase activity (CAT, EC 1.11.1.6) – by the level of hydrogen peroxide degradation [16], glutathione peroxidase activity (GP, EC 1.11.1.9) – by the accumulation of oxidized glutathione in the incubation environment [17]. The concentration of total protein was measured by Bradford method [18]. Superoxide dismutase 1 (SOD1) and nitrotyrosine levels were measured with a commercial rat enzyme immunoassay kits (cat No CSB-EL022397RA, Cusabio biotech co., cat No ab113848, Abcam, UK, respectively) in hippocampus and frontal cortex homogenates. Plasma acetylcholinesterase activity was determined using commercially available multienzyme kit (cat No MAK 119-1KT, Sigma, USA).

The data, presented as mean values ± standard errors of the means (SEM), were compared using the Student’s unpaired t-test. The differences were considered significant at P < 0.05.

Results and Discussion

Behavioral studies. Animals that received scopolamine, compared to the controls, showed a significant memory loss (only 15% of animals in the group within 24 h had a PAR retention) (Fig. 1).

Pretreatment with NSE prevented memory impairment in rats under scopolamine action (Fig. 1). Hence, 43% of rats from “NSE + Scopolamine” group showed PAR retention after 24 h.

![Fig. 1. Effect of N-stearoylethanolamine on the memory of rats: 1 – Control; 2 – Scopolamine; 3 – NSE + Scopolamine](image-url)
This data suggested that NSE prevents rats memory impairment under scopolamine action.

Biochemical studies. Acetylcholinesterase activity in plasma. Activity of acetylcholinesterase (AChE) increased in plasma of rats with experimental cholinergic deficiency induced by scopolamine (Fig. 2). Meanwhile, pretreatment with NSE prevented the increase of plasma AChE activity under the scopolamine action.

SOD and nitrotyrosine protein level and SOD activity in the frontal cortex. The results of our study, presented in Fig. 3 and 4, showed that the SOD level and activity were significantly increased in the frontal cortex of aged rats with scopolamine-induced cognitive impairment. However, scopolamine did not induce any significant changes in the content or activity of SOD in hyppocampus (data are not presented). In addition, obtained results suggest that scopolamine administration to rats triggered a decrease of nitrotyrosine level in the frontal cortex (Fig. 4).

Pretreatment of animals with NSE did not prevent the effect of scopolamine on SOD and nitrotyrosine level, however, prevented the increase of SOD activity in the frontal cortex (Fig. 3).

TBARS level and SOD, KAT, GP activity in plasma. Obtained data showed enhanced accumulation of TBARS in plasma of rats under scopolamine administration (Fig. 5). Also, we have found that activity of all studied antioxidant enzymes (SOD, CAT, GP) was significantly reduced in plasma of aged rats under the influence of scopolamine (Fig. 5, B, C, D). Pretreatment of experimental animals with NSE prevented a decrease in SOD, CAT, GP plasma activity (Fig. 5, B, C, D) and inhibited formation of TBARS (Fig. 5, A).

Total level of phospholipids and level of individual phospholipids in the frontal cortex and hippocampus.

Table represents the level of inorganic phosphorus of total phospholipids in the hippocampus and frontal cortex of rats with experimental cholinergic deficiency.

According to the obtained results (Table), scopolamine administration did not cause significant changes in the content of inorganic phosphorus of total phospholipids in the frontal cortex. In addition, NSE administration also did not affect the level of inorganic phosphorus of total phospholipids.

However, we have found a significant decrease in the content of inorganic phosphorus of total phospholipids in hippocampus of “Scopolamine” group (Table). Pretratment of experimental animals with...
NSE prevented the reduction of inorganic phosphorus level of total phospholipids in the hippocampus. The results of individual phospholipids determination showed that scopolamine administration induced significant changes in the content of main membrane phospholipids – PC, LPC, SM, PS and diphosphatidylglycerol (DPG). Fig. 6 and 7 represent a percentage of each studied individual phospholipid level in the hippocampus and frontal cortex of rats from “Scopolamine” and “NSE+Scopolamine” group.

According to the results from figure 6, scopolamine caused an increase of LPC, SM, PS and decrease of PC and DPG level in rat hippocampus.

The results of current study have shown that NSE administration prevented changes in the level of phosphatidylcholine (PC), lysophosphatidylcholine (LPC), sphingomyelin (SM) and phosphatidylserine (PS) in hippocampus of scopolamine administrated rats, however, NSE did not affect diphosphatidylglycerol (DPG) level (Fig. 6).

The study of phospholipid composition of the frontal cortex indicated that scopolamine administration increased content of SM, DPG and LPC (Fig. 7). Meanwhile, the level of PC was considerably reduced in “Scopolamine” group of rats (Fig. 7). Pretreatment of animals with NSE prevented ob-
Total phospholipid level (mkg P /g tissue) of frontal cortex and hippocampus in control rats and rats with experimental cognitive impairment (M ± m, n = 7)

<table>
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<tr>
<th>Tissue</th>
<th>Intact</th>
<th>Scopolamine</th>
<th>NSE + scopolamine</th>
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<tr>
<td>Frontal cortex</td>
<td>1529.67 ± 53.62</td>
<td>1591.84 ± 23.88</td>
<td>1607.72 ± 24.83</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>1213.24 ± 44.39</td>
<td>1092.92 ± 18.91*</td>
<td>1276.21 ± 62.55#</td>
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Values represent the mean ± SEM (n = 7); * P < 0.05 versus control rats; # P < 0.05 versus scopolamine rats.

Fig. 6. Hippocampus tissue phospholipid composition (% of the total amount of phospholipids): **PC** – phosphatidylcholine; **LPC** – lysophosphatidylcholine; **SM** – sphingomyelin; **PS** – phosphatidylserine; **DPG** – di-phosphatidylglycerol. 1 – Control; 2 – Scopolamine; 3 – NSE + Scopolamine; values represent the mean ± SEM (n = 7); * P < 0.05 versus control rats; # P < 0.05 versus scopolamine rats
served changes in the phospholipid level of the frontal cortex of rats under scopolamine action.

Cholesterol level in the frontal cortex and hippocampus. Fig. 8 represents the level of free and esterified cholesterol level in different parts of the brain from rats with scopolamine treatment. As shown in Fig. 8, A, 2, scopolamine triggered a significant decrease of free cholesterol level in hippocampus. Pretreatment with NSE prevented changes in free cholesterol level in hippocampus of rats caused by scopolamine administration (Fig. 8, A, 2).

Determination of free cholesterol content in the frontal cortex of rats showed a significant increase of free cholesterol level in rats treated with scopolamine (Fig. 8, A, I). Pretreatment of rats with NSE did not eliminate the effect of scopolamine on free cholesterol content (Fig. 8, A, I).

According to our data, presented in Fig. 8, B, scopolamine caused a considerable increase in esterified cholesterol level in rats hippocampus and frontal cortex. Pretreatment with NSE prevented the increase of esterified cholesterol level in the hippocampus, however, no effect in the frontal cortex was found (Fig. 8, B, 2).

This experiment was carried out to evaluate the protective effects of NSE on memory state, blood and brain biochemical parameters in rats under scopolamine-induced cognitive impairment.

It is known that acetylcholine and muscarinic acetylcholine receptors (mAChR) play an important role in learning processes and memory capacity. Previous results showed that M1 mAChR activation by acetylcholine facilitates the induction of synaptic plasticity and enhances cognitive function in rats [19]. On the other hand, behavioral and physiological animal tests showed that the use of muscarinic acetylcholine receptor antagonists (e.g., scopolamine) resulted in decrease of learning and memory ability [20, 21]. Scopolamine increases the activity of AChE in brain tissue and blood [21-23], leading to a rapid cleavage of acetylcholine, a decrease in its concentration and memory loss.

Fig. 7. Frontal cortex tissue phospholipid composition (% of the total amount of phospholipids): PC – phosphatidylcholine; LPC – lysophosphatidylcholine; SM – sphingomyelin; DPG – diphosphatidylglycerol. 1 – Control; 2 – Scopolamine; 3 – NSE + Scopolamine; values represent the mean ± SEM (n = 7); * P < 0.05 versus control rats; # P < 0.05 versus scopolamine rats
Recent studies provide evidence that acetylcholine deficiency is involved in cognitive impairment of both neurodegenerative and vascular origin [24, 25].

Thus, cholinergic dysfunctions, such as reduced cholin uptake, increased AChE activity, decreased acetylcholine synthesis, decreased activity and degeneration of cholinergic neurons in certain brain structures, were associated with a decrease of cognitive function in patients with Alzheimer’s disease (AD) [22, 26].

Numerous experimental studies indicated that the activity of AChE is significantly increased in hippocampus, amygdala and cerebral cortex of patients with AD [27].

Notably, AChE inhibitors, such as donepezil, galantamine and rivastigmine, improved cognition and indirectly increased the quality of life in patients with AD [28], however, they were not able to stop the disease progression and showed little therapeutic activity with a few side effects and contraindications.

Recent findings indicated that some of NAEs are competitive (anandamide) and non-competitive (oleoylethanolamine and palmitoylethanolamine) inhibitors of plasma butyrylcholinesterase (BuChE) [29]. Changes in the level and activity of this enzyme were indicated in the pathogenesis of diseases associated with cognitive disorders (AD, multiple sclerosis) [30, 31].

In addition, it has been found that pretreatment of mice with oleoylethanolamine before scopolamine administration prevents the development of cognitive impairment in animals and promotes the growth of choline acetyltransferase activity (ChAT) [32]. At the same time, there are no evidence about NSE effects on AChE, BuChE and ChAT activity.

The results of this study indicated a significant memory loss and increase of AChE activity in plasma of aged rats with experimental cholinergic deficiency induced by scopolamine (Fig. 1, 2). Pretreatment of experimental animals with NSE prevented the growth of acetylcholinesterase activity in plasma and memory impairment in rats under scopolamine action (Fig. 1, 2). Unfortunately, we did not study the NSE action on the plasma ACHE activity of scopolamine - untreated rats.

As previously reported by us NSE caused a protective effect on brain tissue and improved memory.
capacity of mice injected with lipopolysaccharide or immunized with the extracellular domain of α7 nicotinic acetylcholine receptor [6].

Therefore, we can assume that NAEs may prevent the development of cholinergic dysfunction and cognitive impairment in mammals due to down-regulation of AChE and BuChE, and up-regulation of ChAT activity, hence, modulating the level of acetylcholine.

Oxidative stress is suggested to be one of the molecular mechanisms of cholinergic neurodegeneration and cognitive dysfunction in AD [33]. Scopolamine, an antagonist of muscarinic receptors, exhibits a central inhibition of cholinergic transmission, causing oxidative stress development in brain and enhanced memory loss in humans and animals [22, 34]. Additionally, it has been shown that scopolamine induced down-regulation of neurogenesis, a significant increase of acetylcholinesterase activity and nitric oxide level (enhanced expression of iNOS), accumulation of TBARS (malonic dialdehyde), and a decrease of antioxidant enzymes activity (SOD, CAT, GP) in the hippocampus and cerebral cortex of rats and mice [35]. In addition, scopolamine mediated enhanced formation of reactive oxygen species, a decrease in antioxidants level, an increase of plasma and serum nitric oxide level in animals [35]. Thus, pathogenesis of cholinergic neurodegeneration and development of cognitive impairment induced by scopolamine, is associated with oxidative/nitrosative stress, impaired pro-/antioxidant balance in brain tissue and blood samples from humans and animals.

The results of our study showed a significant increase of SOD level and its activity, as well as decrease level of nitrotyrosine in the frontal cortex but not in hippocampus of aged rats with scopolamine - induced cognitive impairment (Fig. 3, 4). Also, obtained data showed a remarkable reduce of SOD, CAT, GP activity and enhanced accumulation of TBARS in plasma of rats under scopolamine administration (Fig. 5).

Pretreatment of experimental animals with NSE prevented the increase of SOD activity but did not prevent the effect of scopolamine on SOD and nitrotyrosine level in the frontal cortex (Fig. 3, 4). Also, NSE inhibited formation of TBARS and prevented decrease in SOD, CAT and GP activity in plasma (Fig. 5).

These results agreed with earlier published data where antioxidant enzymes (SOD, CAT and GP) activity was down-regulated in brain tissue during neurodegenerative diseases [33].

It has been known that NAEs, particularly NSE, exhibit adaptogenic, membrane-protective, antioxidant, immunomodulatory, anti-inflammatory, anti-allergic and anti-toxic effects [36]. Additionally, NSE modulated nitric oxide level (by affecting activity of constitutive and inducible NO synthases under different pathological conditions) [37] and reactive oxygen species level (by reducing the production of superoxide anion under LPS treatment) [38]. It worth to mentioning that effect of NSE is observed only under pathological conditions and does not show up under healthy normal conditions [39, 40]. Consequently, NSE prevented scopolamine-induced memory impairment in rats, by changes in pro-/antioxidant balance in brain tissue and blood samples.

It is known that brain is one of the richest tissues in total lipid level, and any changes in brain lipid composition can lead to the development of various pathological processes.

Recently, many studies have indicated disturbances in lipid profile of hippocampus and other brain structures, cerebrospinal fluid and plasma during AD [41-43]. Mainly these changes were associated with the basic phospholipids, such as PC, phosphatidylethanolamine (PE), PS, SM, phosphatidylinositol (PI), as well as free fatty acid and phospholipids’ fatty acid composition, and cholesterol level [42-45]. It is suggested that phospholipid level in plasma and cerebrospinal fluid may contribute to early detection, risk assessment and therapeutic monitoring of mild cognitive impairment and dementia in AD patients [41].

AD development is correlated with the metabolism of β-amyloid precursor protein (APP), which is closely related to changes in membrane lipid composition [42]. Secretases and APP are integral proteins, hence their lipid environment can play a significant role in protein metabolism and as a result in beta amyloid (Aβ) generation [46, 47].

Therefore, drugs that block muscarinic cholinergic neurotransmission may stimulate Aβ formation and decrease the level of PC in the brain (down-regulating its synthesis and activating its decay). These effects can reduce a number of brain synapses and might cuse memory disorders in early stages of AD [48]. Furthermore, agents that inhibit acetylcholinesterase (e.g., rivastigmine) modulated plasma phospholipid profile decreasing choline-containing phospholipids level [49].

It has been found that administration of PC to mice with dementia caused an increase of ace-
Thus, n-3 PI and PS significantly diminished scopolamine-induced amnesia [51]. Consequently, the drug administration may cause preservation or restoration of structural and functional integrity of individual brain structures as well as the whole brain, and should prevent the development of neurodegenerative disorders and loss of cognitive ability.

In conclusion, biologically active compounds—N-acetyl-ethanolamines are the promising drug candidates.

The study of phospholipid content of hippocampus and frontal cortex of rat brain under scopolamine action showed a significant decrease in the content of inorganic phosphorus of total phospholipids in hippocampus, and remarkable changes in the content of main membrane phospholipids (Table, Fig. 6, 7). Pretreatment with NSE prevents changes in total content of phospholipids in the hippocampus and changes in the main individual phospholipid levels, such as PC, LPC, SM, PS and DPG in the hippocampus and frontal cortex of aged rats (Table, Fig. 6, 7). The revealed protective effect of NSE on the phospholipid composition of the studied brain structures may mediate its protective effect on memory state (Fig. 1).

Nowadays, it is well known that cholesterol is vital for normal brain function, synaptic plasticity, training and memory [52].

Considering the published data, pathogenesis of numerous cognitive disorders, including AD, Parkinson's disease, Niemann-Pick disease, Huntington's disease, vascular dementia, etc., were correlated with the disturbances of cholesterol metabolism [53-56]. It has been shown that accumulation of cholesterol in hippocampal neurons lead to changes in lipoprotein homeostasis, hippocampal atrophy and cognitive impairment [57]. In addition, the decrease of the cholesterol synthesis in brain was associated with memory loss [53]. Moreover, the nicotinic and muscarinic acetylcholine receptors, Na/K-ATPase, adenylate cyclase, calcium homeostasis, formation and aggregation of Aβ are cholesterol-dependent [58-60].

Based on the results, scopolamine cased a considerable changes in free and esterified cholesterol level in different parts of aged rat's brain (Fig. 8). Pretreatment with NSE prevented changes in the level of free cholesterol and its esterified form in hippocampus, and level of free cholesterol in frontal cortex of rat brain (Fig. 8). Thus, NSE is able to modulate the level of free and esterified cholesterol in different parts of rat brain with cholinergic deficiency. We suggest that moderate protective effect of NSE on memory was partly associated with its modulatory action on free and esterified cholesterol level in different brain sections of rats under scopolamine action.

In addition to already known properties of NSE (adaptogenic, neuroprotective and anti-inflammatory properties, inhibition of FAAH-mediated hydrolysis of anandamide and modulation of the permeability of the blood-brain barrier), our results revealed that NSE also prevented a memory loss and an increase of acetycholinesterase activity, imbalance of antioxidant system in plasma, hippocampus and frontal cortex of rats, changes in phospholipid composition, free cholesterol and esterified cholesterol level in studied brain structures. Taking into account that NSE is a member of endocannabinoid system, the obtained data also provided a clear understanding of the endocannabinoids protective role under the cognitive impairment. Therefore, the results of this study can form the basis for considering NSE as a promising tool in drug development for prevention and treatment of cognitive impairment of different profiles.

**T. M. Horid’ko, H. V. Kosiakova, A. G. Berdyshiev et al.**

**ПРЕВЕНТИВНА ДІЯ N-СТЕАРОЇЛЕТАНОЛАМІНУ НА РОЗВИТОК ПОРУШЕНЬ ПАМ’ЯТІ, БІОХІМІЧНІ ПАРАМЕТРИ КРОВІ ТА МОЗКУ В ЩУРІВ З ЕКСПЕРИМЕНТАЛЬНИМИ СКОПОЛАМІНІНДУКОВАНИМИ КОГНІТИВНИМИ ПОРУШЕННЯМИ**

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Порушення когнітивних функцій є найактуальнішою медичною та соціальною проблемою сьогодення. Метою роботи було оцин-
Протекторний вплив N-стеароїлетаноламіну (NSE) на стан пам'яті, біохімічні показники крові та головного мозку у щурів при індукованих скополаміном когнітивних розладах. Результати досліджень показали, що NSE за умов введення його щурам per os (5 мг/кг, 5 днів, протягом останніх 3 днів за 20 хв до введення скополаміну (1 мг/кг, одні раз на добу протягом 3 днів, інтра- перитонеально)) запобігає розвитку порушення пам'яті. Виявлений ефект NSE може бути обумовлений його здатністю запобігати зростанню ацетилхолінестеразної активності, порушенню про/антіоксидантної рівноваги в плазмі крові, гіпокампі та фронтальній корі головного мозку тварин, змінам вмісту фосфоліпідів, вільного холестеролу та його ефірів у досліджуваних відділах головного мозку щурів. Виявлені ефекти NSE можуть бути обумовлені його здатністю запобігати зростанню ацетилхолінестеразної активності, порушенню про/антіоксидантної рівноваги в плазмі крові, гіпокампі та фронтальній корі головного мозку тварин, змінам вмісту фосфоліпідів, вільного холестеролу та його ефірів у досліджуваних відділах головного мозку щурів. Виявлені ефекти NSE можуть бути обумовлені його здатністю запобігати зростанню ацетилхолінестеразної активності, порушенню про/антіоксидантної рівноваги в плазмі крові, гіпокампі та фронтальній корі головного мозку тварин, змінам вмісту фосфоліпідів, вільного холестеролу та його ефірів у досліджуваних відділах головного мозку щурів. Нарешті, виявлені ефекти NSE можуть бути обумовлені його здатністю запобігати зростанню ацетилхолінестеразної активності, порушенню про/антіоксидантної рівноваги в плазмі крові, гіпокампі та фронтальній корі головного мозку тварин, змінам вмісту фосфоліпідів, вільного холестеролу та його ефірів у досліджуваних відділах головного мозку щурів.


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