Review Article

A systematic review of the role of gummosin Gummosis in improving memory in the scopolamine memory impairment model

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ABSTRACT

In this study, the role of gummosin in improving memory in the scopolamine memory impairment model was systematically examined. Memory and learning are the most developed and complex functions of the nervous system. Learning is the acquisition of new information that occurs as a change in behavior, and memory is the ability to store and retrieve learned information. In other words, memory is a combination of various processes of information acquisition, consolidation, storage and retrieval. The processes of memory consolidation and storage are the result of a series of time-dependent neurobiological events that occur after the initial formation of memory. In addition, this fluctuation of processes related to memory storage can fully occur shortly after the initial learning experience. Memory is a direct result of learning ,as it stores and retrieves learned experiences and information. The results of our study show that scopolamine leads to impaired memory, learning and synaptic plasticity, which is associated with a change in the expression of various genes and a reduction in the number of hippocampal neurons. The disorders that occurred in the rats of the scopolamine group confirm the model used in this study to induce memory and learning deficits, which is consistent with previous studies confirming the model used to induce Alzheimer's disease. The results of the behavioral tests in this study showed that, consistent with previous work, scopolamine caused a significant increase in anxiety behavior that was associated with a decrease in time spent in the central area compared to the control group, while donepezil injection resulted in a decrease in anxiety behavior. The time spent in the central area was increased compared to the scopolamine group.

Keywords: Gummosin, Learning, Memory, Scopolamine.

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1. Introduction

Although there is an immediate motor response to some sensory information, most of the information remains in the brain, where it is stored and used for reasoning and information retrieval. This storage of information, which largely takes place in the cerebral cortex, is called memory (1). In other words, reflective memory is a combination of various processes of information acquisition, consolidation, storage, and recall that form the main stages of learning and memory (2). The absorption of information from the variable environment is the acquisition phase. The consolidation and storage processes allow information to be retained for hours, days and even years. Since memory can be destroyed or reinforced during the consolidation phase, this phase is very unstable and allows memory to integrate with new experiences. The processes of memory consolidation and retention are the result of a series of time-dependent neurobiological events that occur after initial memory formation (3,4). In addition, this fluctuation of processes related to memory storage can fully occur shortly after the initial learning experience. Finally, the stored information is retrieved in the retrieval phase. Different structures of the brain are involved in the different phases of memory. Studies show that the areas of the left hemisphere of the brain are generally activated during the acquisition phase, while most of the right hemisphere is activated during the retrieval phase, so that the distinction between the acquisition and retrieval phases has a specific biological basis (5,6). It should be noted that memory is divided into three main types: sensory, short-term and long-term memory. Sensory memory becomes short-term memory with appropriate attention, and short-term memory becomes long-term memory with practice and consolidation. Memories can be forgotten at any stage of sensory memory, whether short-term or long-term (7,8).

1.1. Sensory memory

Sensory memory is the first stage of information processing when external stimuli are received by the senses. Sensory memory stores sensory information for a short period of time and becomes short-term memory (9,10). This type of memory is beyond conscious control and the length of time information is stored in this memory varies from a few milliseconds to a few seconds. This memory exists for each sensory channel and includes the iconic memory for visual stimuli, the echoic memory for auditory stimuli and the haptic memory for the sense of touch.

1.2. Short term memory

Short-term memory refers to memory processes in which information is temporarily stored until it is forgotten or added to stable long-term memory, and lasts between seconds and hours. The capacity of this type of memory is very limited and comprises an average of 7±2 elements. The capacity of this type of memory can be increased by the fragmentation process. The time in which information can be retained can also be increased through practice. Some researchers consider short-term memory and working memory to be one and the same, while others consider working memory to be part of short-term memory. Working memory refers to the structures and processes used for the temporary storage and manipulation of information (11,13), while short-term memory refers to the short-term storage of information and does not involve manipulation and reorganization in memory. When short-term memory is combined with other mental processes, working memory is activated.

1.3. Long-term memory

Information is transferred from short-term memory to long-term memory through repetition and mental review. In contrast to short-term memory, the capacity of long-term memory is unlimited. The storage duration of information ranges from a few days to a few years and even until the end of life. Long-term memory is formed when certain neuronal connections are permanently and reliably strengthened. In short-term memory, memory content can be destroyed and disrupted by trauma or various drugs, whereas long-term memory is remarkably resistant to damage Long-term memory not only modulates function but also alters synaptic structures depending on specific gene expression patterns. Therefore, blocking the transcription or translation of these genes can halt long-term memory. Long-term memory is divided into two types: expressive and non-expressive memory (Figure 1).

1.3.1. Expressive memory (conscious or news):

This is a memory that refers to facts, thoughts and events that can be consciously remembered. The concept that people usually have in mind when they hear the word memory is this type of memory. Verbal memory is linked to consciousness, or at least to awareness, and relies on the hippocampus and other parts of the middle temporal lobe of the brain for storage. Expressive memory is divided into two types: implicit or event memory for events and semantic memory for facts (15).

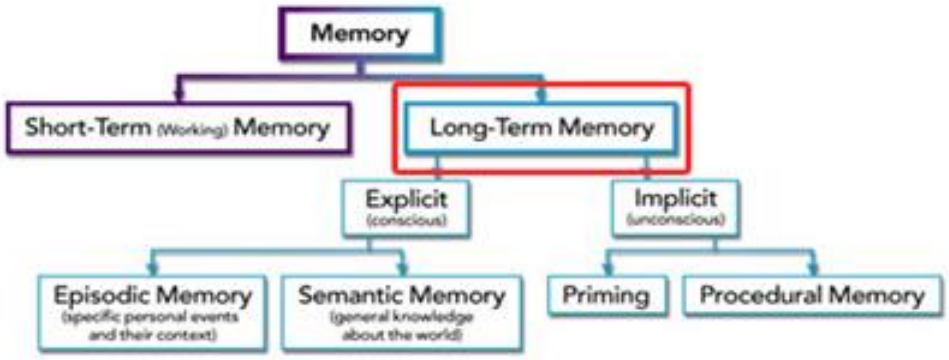

Figure 1. Classification of long-term memory

1.3.2. Non-expressive memory (unconscious or non-informative):

Non-expressive or conceptual memory, unlike expressive memory, is not conscious and is not associated with awareness and attention. It therefore does not require the hippocampus for processing. This memory is widespread and involves the formation of habits and learning processes. Conceptual memory itself is divided into four types and includes executive memory, initiator memory, non-associative learning and relational learning (16).

1.4. Spatial memory

Spatial memory, which includes working memory and reference memory, enables humans and animals to recognize a situation in space based on spatial cues. In other words, spatial memory is a memory that stores information about the physical location of objects in space or the spatial features of the environment. A specific behavioral response that relies on spatial memory is orientation, which involves the ability to move from one place to another, which is an observable and measurable behavior for studying spatial memory (17). In animals and humans, spatial memory is summarized as a cognitive map. In cognitive map theory, the hippocampus is considered a location where spatial information is stored and is frequently used for orientation (18). The hippocampus and structures such as the amygdala play an important role in learning and in the formation of spatial memory, but there is much evidence that the right hippocampus plays the main role in spatial memory. In the hippocampus, there are place cell structures, mainly present in the CA1 and CA3 regions of the hippocampus, which ensure that a spatial structure is formed in the hippocampus from the environment. In addition to these two regions, the dentate gyrus in the hippocampus also plays a role in memory encoding and also separates spatial patterns from each other (19). Nowadays, various methods are used to test spatial memory. Some of these methods are more recent and more commonly used, including the Y-shaped maze test, the 8-arm radial maze test, and the Morris water maze test (20).

1.5. Morris water maze test

The Morris water maze is one of the tests invented by Morris and his colleagues in 1982 and used for learning and spatial memory in rodents. This test shows well the effects of memory improvement or forgetfulness depending on the function of the hippocampus. In this test, the animal is placed in a pool of water and must remember the location of the platform, which is located directly under the water, using signs and visual cues located outside the maze (21). This method is based on the fact that the animals have found a suitable strategy to search their environment and escape from danger, where they can achieve the desired result with minimal effort. In this test, parameters such as the time taken to find the platform, the total distance traveled to find the platform, the speed of movement of the mouse in each training session, the total distance traveled, and the time the animal spends in each quadrant of the circle are used to determine the performance of the mice. Compared to other mazes, the Morris water maze method has several advantages, one of which is that it reduces the possibility of auditory and olfactory interference, and another advantage is that the animals can learn easily and simply in this maze (22). Despite many advantages of the water maze, this maze can also have disadvantages, such as stress for the animal in the maze environment (23).

1.6. Forgetfulness

Forgetfulness occurs for a variety of reasons, and most normal everyday forgetfulness is related to different stages of memory. When a problem occurs in one of the memory

stages, it is difficult to recall information. If an error occurs in the encoding or data storage phase. This means that the memory does not have the necessary conditions to encode the information correctly. It is possible that a lack of attention when storing information is the cause of this error (24). If the error occurs in the process of consolidation and storage, the information is not stored correctly and completely or is not stored in the right place. One of the factors that enables the consolidation of information is mental review. Mental review helps to consolidate the information in memory and retain it for longer. In the recall stage, factors, such as interference and emotional factors impede the retrieval of information (25). If different pieces of information are stored in our memory with a common cue, when we use that cue to recall one of piece of information, other information will come to mind and interfere with the recall of the desired information. Since only a small part of the information we receive is useful, the brain needs a mechanism to free itself from the heavy burden of useless information, i.e., to forget it. Newly learned information is highly susceptible to destruction after acquisition, which is referred to as retroactive forgetting (26). While the inability to learn new information is called prospective amnesia, a condition in which a person can retain a small amount of information for a short period of time but has trouble with longer memories. Therefore, short-term memory preserves information from being forgotten in the future. In addition, memories can be modulated by reconsolidation. Memory erasure is another process that suppresses rather than erases early learning. In this type of active learning, new memories are formed while the original memory remains intact. The prefrontal cortex and the glutamatergic system appear to play a role in memory extinction (27).

1.7. Neuro anatomo physiology of learning and memory

During short-term working memory, the prefrontal cortex and the medial temporal lobe play the main role, while during storage from short-term to long-term memory, the hippocampus and the cortical region of the temporal lobe are involved. Many brain regions are involved in long-term memory, and memory is increasingly formed by linking the information from all these brain regions. A memory needs time to stabilize in the hippocampus before it is finally stored. After stabilization, the memory moves from the hippocampus to the corresponding brain regions and remains there for a long time. In the memory retrieval phase, the information is retrieved from the corresponding areas. In the case of younger memories, integration takes place with the help of the hippocampus; in the case of older memories, this integration is independent of the hippocampus (28).

2. Hippocampus

The hippocampus is part of the limbic system and an important subcortical structure in mammals, which appears to play an important role in the memory and learning process in rats and other mammals. Surrounding the hippocampus are tissues called the hippocampal complex, which include the hippocampal body (CA), dentate gyrus, and para hippocampal gyrus (Figure 2). The hippocampus can be divided into four main areas CA_4-CA_1. The CA_3 and CA_4 regions make up the largest part of the hippocampus. The CA_2 region is so small in some species that it is usually overlooked. The CA_1 area of the hippocampus is the most complex part of the hippocampus. In addition to pyramidal neurons, this area contains at least two types of inhibitory interface neurons, including basket cells and O/A cells (29). Studies have shown that the hippocampus plays a role in the conversion of short-term to long-term memory. Damage to the hippocampus results in a person no longer being able to remember things in their long-term memory. Damage to the hippocampus leads to learning disorders humans learning, and damage to the amyloid and hippocampus leads to the loss of a large part of memory. Studies have shown that of the different areas of the hippocampus, the CA1 and dentate gyrus play a greater role in spatial learning (30). The destruction of the hippocampus in animals has shown various effects on behavior, including increased general activity, a reduction in spatial memory and cognitive function, and impaired learning and memory, particularly in retaining new memories. In addition, it was found that while damage to the hippocampus is sufficient to trigger amnesia, damage to entorhinal cortex areas exacerbates the effects of amnesia, suggesting that most afferents from the cortex reach the hippocampus via this area. It is worth noting that the hippocampus plays a role in the acquisition and retrieval of spatial memory. Therefore, creatures that require greater spatial memory have a larger hippocampus, larger hippocampal cells and more connections (31). There are many neurotransmitters in the hippocampus, such as GABA, glutamateand aspartic acid. In addition, the hippocampus also contains the neurotransmitters acetylcholine, noradrenaline, dopamine, serotonin and histamine. Since the hippocampus has the highest concentration of excitatory amino acid receptors in the brain, it is more vulnerable than other parts of the brain

(32). In the hippocampus, there is a stronger link between behavioral disorders and the reduction of acetylcholine

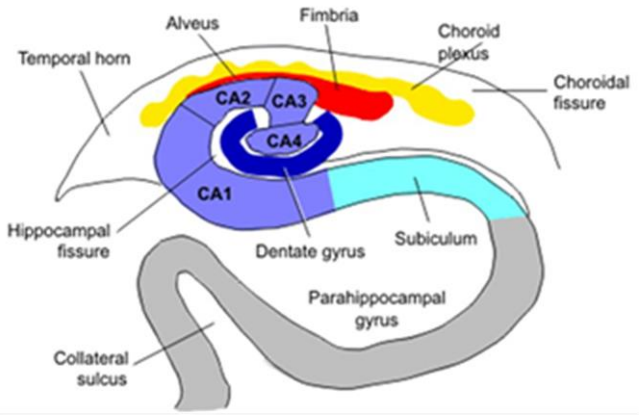

Figure 2. A view of the anatomy of the hippocampus

transferase than in the cortex, and the destruction of certain parts of the hippocampus is sufficient to destroy memory and learning. These findings suggest that the hippocampus is a sensitive area for the control of memory and learning processes (33,35). Studies show that there is a close link between neurogenesis in the adult hippocampus and learning and memory processes, such that newly formed neurons can be integrated into the neuronal cycles associated with learning in the hippocampus. In addition, these neurons are involved in learning and memory processes at every stage of maturity. Many neurological diseases such as depression, epilepsy, Alzheimer's and Parkinson's can affect neurogenesis in the hippocampus. In addition, the hippocampus is the brain region that is most sensitive to oxygen deprivation and anemia due to injury. Studies show that reduced or damaged hippocampal volume is associated with many psychiatric disorders, including bipolar disorder, post-traumatic stress disorder and depression (36, 38).

3. Cellular-molecular mechanisms of learning and memory

Synaptic plasticity is a change in the strength of synaptic function, and this process is directly related to memory formation. Synaptic plasticity involves both short-term changes in the strength of synaptic transmission efficiency and long-term changes in the structure and number of synapses (39,41). Learning induces cellular-molecular changes and ultimately strengthens or inhibits interneuron communication. If learning induces changes in the synaptic strength of interneuronal circuits, then the maintenance of these changes explains how memories are stored. In 1973, it was first observed that continuous stimulation of afferent fibers leads to long-term potentiation of synaptic transmission. This phenomenon has been termed long-term potentiation (LTP) and its reverse process, long-term attenuation (LTD). These two processes cause changes in synaptic strength known as synaptic plasticity. In fact, the physical structure of memory may be a form of synaptic plasticity (42). Today, these two processes are the main known mechanisms for modulating and regulating synaptic plasticity. It should be noted that LTP in the hippocampus has two phases: early LTP and delayed LTP. In the early phase, which lasts one to three hours, no protein synthesis takes place. If stimulation is increased, LTP enters a delayed phase, which lasts longer, and new proteins are formed during this phase. In contrast to the early phase, in which separate pre- and postsynaptic changes occur, the delayed phase requires coordinated structural changes that occur through the activity of forward and reverse sequences in the pre- and post-synaptic neuron (43). Glutamate and NMDA receptors are necessary to induce LTP. Short-term memory induces functional changes in neuronal networks through appropriate regulation of intracellular message systems. These short-term changes can undergo one of two processes: they either disappear over time, or they are reinforced and pass into long-term memory during the consolidation process. During the stabilization phase, functional changes cause gene transcription and protein synthesis, leading to permanent structural changes in neurons and neuronal networks. In short-term memory, proteins are influenced by post-translational processing and changes in synapse strength, while long-term memory formation requires the synthesis of new proteins and the development of connections. The molecular processes involved in short-term memory include the following (44):

3.1. Change in stimulation and exocytosis of the presynaptic neuron, which occurs by altering the conduction of the neuron, which is the result of phosphorylation and calcium influx.

3.2. The influx of calcium via NMDA receptors into the postsynaptic neuron with the help of calcium-calmodulin kinases (CaMK), protein kinase C (PKC and tyrosine kinase), phosphorylates neurotransmitter receptors and causes the production of messenger substances, such as nitric oxide, which activates the terminal of the

presynaptic axon and thus increases the release of neurotransmitters.

The activity of the signaling pathway molecules persists for several minutes and generates short-term memory. It should be noted that phosphorylation has a half-life that depends on the kinetics of dephosphorylation by phosphatases. The balance between calcium/calmodulin kinase II (CaMKII) and protein phosphatase I (PPI) plays an important role in the formation of short-term memory. During memory formation, CaMKII is autophosphorylated and active by the introduction of calcein, which can be restored to its initial state by PPI, which plays an inhibitory role in learning (45). These changes cannot persist for long if there is no neuronal reorganization at the synapse in question. The continuous activation of similar pathways leads to a memory

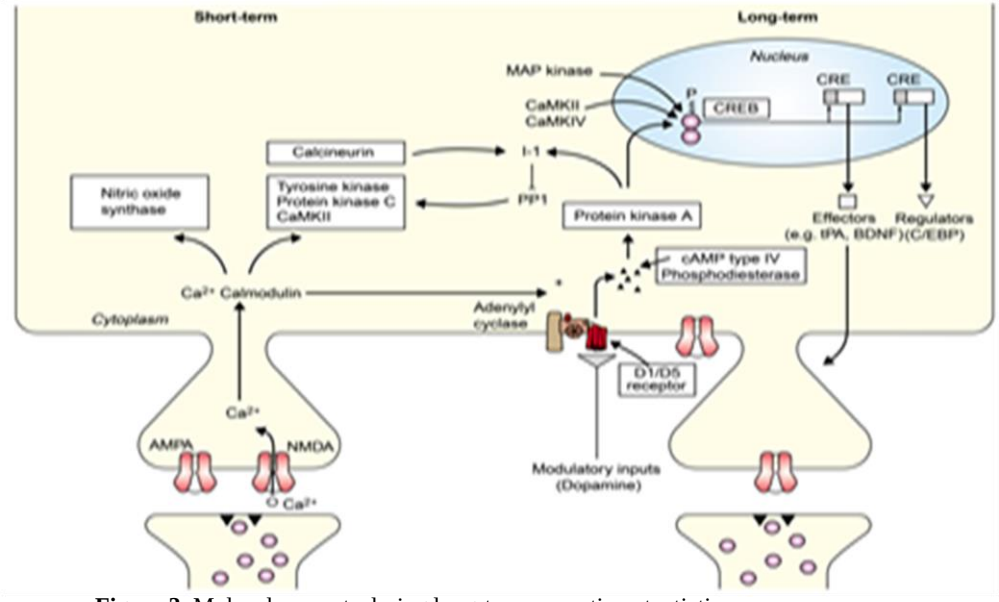

Figure 3. Molecular events during long-term synaptic potentiation

initially neutral to the animal, is presented immediately before the unconditioned stimulus. The amygdala and the consolidation of memory through transcription and translation. In addition, continuous stimulation causes stable activity of protein kinase A (PKA) and MAPK, which cause phosphorylation and activation of the transcription factor CREB. The proteins produced may play a role in the synthesis of other proteins, axon growth, synapse structure and function (46). When synaptic strength increases, ribosomal proteins, neurotrophies, calcium-binding proteins, proteins involved in exocytosis, and neurotransmitter receptors are upregulated, while adhesion molecules that normally establish a stable state for the synapse downregulated. are downregulated. These specific changes in the expression of proteins cause the growth of the axon terminal and its branches as well as the formation of new synaptic connections. The reverse process takes place during long-term attenuation, which reduces synaptic strength. The molecular mechanisms in the individual phases of memory are as follows:

3.3. Memory acquisition:

the molecular events that take place during memory mianly include mechanisms that can be observed in the acquisition phase. One of the most important of these mechanisms, for example, is LTP, a type of synaptic plasticity. Many studies dealing with the mechanisms of associative learning have focused on fear conditioning. In fear conditioning, the conditioning stimulus, which is hippocampus are the two main sites involved in this type of learning. At the molecular level, NMDA receptors are required for this learning. This is because the deletion of the gene encoding the R1 subunit of NMDA receptors in the CA1 region of the hippocampus causes deficits in associative learning (47).

3.4. Consolidation and storage of memory: In addition to NMDA receptors, the consolidation phase is highly

dependent on AMPA receptors, so inhibition of these receptors in the consolidation phase leads to impaired retrieval of information (48). PKA, through the creation of the transcription factor CREB, play a key role in the cascade events that cause gene expression and synthesis of new proteins during the acquisition and stabilization phases. Therefore, the stabilization phase initiates a wave of protein synthesis and gene expression. During the stabilization phase, different signaling pathways are activated at different time periods. For example, it has been found that the ERK/MAP kinase cascade, which is important for LTP, is activated in the amygdala 60 minutes after fear conditioning and that PKA activity and the amounts of phosphorylated CREB increase three and six hours after training (49).

4. The role of the glutamate system in memory and learning

The first studies in this field were conducted by Colling Ridge and McLennan by manipulating the NMDA receptors in the hippocampus through pharmacological experiments or genetic experiments and found that learning is destroyed by the manipulations. It was also found that blocking NMDA receptors in the hippocampus destroys learning of situations or fear. Although the relationship between NMDA receptors and spatial or situational learning was initially thought to be unique to the hippocampus, other studies have shown that the effects of blocking NMDA receptors on learning are more general and can also be observed in other neuronal structures such as the amygdala. In neuroscience, glutamate is an important neurotransmitter that plays a key role in the development of long-term potentiation (LTP), which is important for learning and memory (50). Glutamate is the most important neurotransmitter in fast synaptic transmission. Almost all brain cells use the neurotransmitter glutamate to transmit messages, and it plays an important role in synaptic flexibility, learning, memory and other cognitive functions. Glutamate is considered the major excitatory neurotransmitter of the hippocampus and CNS, and NMDA and non-NMDA glutamate receptors are activated by this mediator. The most important subunits of NMDA receptors include the NR2A, NR1 and NR2B subunits, which play an important role in spatial learning. MK801, a non-selective antagonist of NMDA receptors, blocks these receptors and thereby reduces learning ability. The activity of NMDA receptors leads to an increase in intracellular calcium levels, which in turn triggers a cascade of intracellular signals and increases synaptic activity in the hippocampus and, leading to the development of a long-term strengthening process. LTP is one of the most important models of synaptic plasticity and is associated with memory consolidation. In studies, scientists have shown that the deletion of the NR_2A subunit leads to disturbances causes disorders in synaptic plasticity and to learning defects. The NR1 subunit in the hippocampus can also generates long-term memory, and the role of this subunit in memory formation is of great interest. On the other hand, increasing the expression of the NR2B subunit in the hippocampus strengthens spatial memory. It has been shown that the expression of the NR2B subunit in the hippocampus of Alzheimer's patients is reduced compared to healthy people (51).

5. An overview of the research done

Based on the research, very few studies have evaluated the effect of gomosin on various biological processes, particularly memory and learning. The only study that has examined the effects of gomosin is the 2019 study by Iranshahy et al. that examined the cytotoxic effects of this compound on breast and prostate cancer cell lines (66-68). This chapter therefore examines studies on the effects of the ferula plant and its coumarin derivatives on memory and learning. In the study conducted by Abdi et al. 2019 (Iran), the effect of ethanol extract of Ferula szowitsiana on cognitive defects and lipid peroxidation caused by ethidium bromide was investigated in an experimental model of MS. The results showed that in the experimental model of MS group, the distance traveled (1022.44±53.29) and the time to reach the hidden platform (41.30±3.29) increased compared to the distance traveled (885.94±29.56) and the time to reach the hidden platform (36.26±0.65) in the control group. Short-term treatment with Ferula szowitsiana extract decreased the distance traveled (838.39±24.16) and the time to reach the hidden platform in these models (39.87±1.24). The MDA value increased in the experimental model of the MS group (0.51±3.8) compared to the control group (0.13±0.68) and decreased in the Ferula-treated group (0.04±0.34) compared to the MS animals. The results show that treatment with an extract of Ferula szowitsiana prevents the deterioration of memory and learning ability by inhibiting lipid peroxidation in an experimental model of MS (52). In the study by Narayanan et al. from 2017 (India), the psychopharmacological properties of the effects of Ferula asafoetida linn were investigated in mice in the Y-maze, EPM and open field. A dose of 400 mg/day of asafetida orally improved memory compared to 200 mg/day in rats. asafoetida showed a stronger effect in improving memory than donepezil and vitamin C. After 11 days of daily treatment with commercially available asafetida powder, more than 50% of the mice showed an increase in the recognition index compared to 0.55 at the

beginning. The results showed that asafoetida powder has a nootropic effect in a mouse model (53). In the study by Nazir et al. 2021 (Pakistan), the phytochemical analysis, anticholinesterase, in vitro antioxidant activity and in vivo nootropic effect of Ferula ammoniacum (Dorema ammoniacum) D. Don. It has been studied in scopolamine-induced memory impairment in mice. The extracts of ethyl acetate (Fa.EtAc) and chloroform fraction (Fa.Chf) inhibited AChE and BChE most strongly with IC50 values of 40 and 43 µg/ml and 41 and 42 µg/ml, respectively. Extract doses of 100 and 200 mg/kg body weight significantly improved short-term memory by increasing the percentage of spontaneous alternation in the Y-maze test as well as the discrimination index in the NORT test, clearly indicating an improvement in the rats' recognition memory. The results show that the extracts were more potent in destroying the tested free radicals and exhibited anticholinesterase activity, improving learning ability, and reducing scopolamine-induced memory impairment in a mouse model. This shows that these extracts can be effectively used to treat oxidative stress, neurodegenerative diseases, neurological diseases and memory loss (54). A 2016 study by Safari et al. examined the transcriptome of genes associated with immunity, antioxidants, mucosal growth and the non-specific immune response of carp fed a Ferula diet. In this eight-week clinical trial, the Anousheh plant increased the expression of antioxidant genes (GSR and GSTA). The results showed that the presence of this plant in the diet significantly increased the activity of lysozyme. However, the evaluations showed no significant decrease in Ig and protease activity in the control and treated groups (55,56). In a 2003 study by Saya et al. entitled "The anticonvulsant effect of Ferula gummosin Boiss extract against experimental seizures", the anticonvulsant activities, neurological defects and lethality of the root extract of this plant were investigated in mice. In this study, the extract of Ferula gummosin showed a dose-dependent prevention of tonic convulsions caused by pentylenetetrazol. However, this extract caused sedation and motor impairment with a TD50 value of 546 mg/kg. Preliminary phytochemical analyzes showed the presence of terpenoids, alkaloids and a small amount of cardenolide in the extract. It appears that the anticonvulsant and neurotoxic effects of the extract are partly related to terpenoid compounds. The results showed that Ferula gummosin Boiss extract calmed and reduced seizures in Syrian rats and improved brain function (57). A 2017 study by Sadeghnia et al. investigated the effects of a standardized extract of Ferula gummosin on glutamate-induced neurotoxicity. In this study, the neuroprotective effect of Ferula gummosin root extract against oxidative stress caused by glutamate was investigated in rat adrenal pheochromocytoma (PC_{12}) and mouse neuroblastoma (N_2a) cell lines. The cells were pretreated with the extract for 2 hours and then exposed to glutamate for 24 hours. After 24 hours, the levels of malondialdehyde (MDA), reactive oxygen species (ROS) and apoptotic cells were determined in both cell lines. The results showed that glutamate increased lipid peroxidation, ROS and apoptotic cells in both cell lines. The extract significantly increased cell viability and reduced ROS production under glutamate-induced oxidative stress in these cells. In addition, the extract decreased MDA levels and apoptotic cells. The results showed that Ferula gummosin root may have a protective effect on glutamate-induced toxicity, suggesting that this extract protects neurons from glutamate-induced oxidative stress (57). In 2013 study by Motai et al. sesquiterpene coumarins extracted from Ferula fukanensis and their inhibitory effects on gene expression of proinflammatory cytokines were investigated. In this study, six novel sesquiterpene coumarin derivatives were isolated from an 80% aqueous methanolic extract of Ferula fukanensis roots. Sesquiterpene coumarin derivatives inhibited the gene expression of nitric oxide (NO) and inducible NO synthase (iNOS), interleukin 6 (IL-6) and tumor necrosis factorα (TNF-α) in a macrophage cell line induced by lipopolysaccharide (LPS) and activated recombinant rat interferon γ (IFN-γ) was activated (58). In the study by Rahimi-Madiseh et al. in 2022 (Iran), the role of NMDA receptor in the anticonvulsant effect of ellagic acid (EA) in pentylenetetrazol (PTZ)-induced seizures in male rats was investigated. The results showed that EA increased the seizure threshold and decreased the expression of Nr_2a and Nr2b. This study showed that ketamine enhances and NMDA reduces the effect of subeffective and effective doses of ellagic acid. Consequently, EA has an anticonvulsant effect on PTZ-induced seizures in rats, possibly by attenuating the NMDA-R signaling pathway. In the 2015 study by Bagheri et al. (Iran), the effect of asafetida on the prevention and treatment of d-Galactose and $NaNO_2$ -induced memory impairment in mice was investigated. In this study, the avoidance response in practice tests 1 and 3 weeks later was significantly increased in the NC (normal control), DP (dementia prophylactic) and DT (dementia treatment) groups compared to the DC (dementia control) group. It is noteworthy that the transit latency was significantly higher in all groups than in the DC group. The total time spent in the bright room, indicating the ability to retain memories, was significantly higher in the DP, NC and DT groups than in the DC group. The results of this study show that asafetida can prevent and treat amnesia. These positive effects may be

related to the efficacy of compounds such as ferulic acid and coumarin derivatives of amblyferon (59). In a study conducted by Huang et al. in 2022 (China), the neuroprotective effect of asafetida (ASF) on oxidative stress-induced apoptosis via the PI3K/Akt/GSK3β/Nrf2/HO-1 pathway was investigated. In-vivo, ASF treatment significantly improved scopolamine-induced cognitive impairment. As well as improving learning and memory abilities, there was a reduction in nerve damage, cholinergic system dysfunction, oxidative stress and apoptosis in the mouse hippocampus. In vitro, the results of this study confirmed that ASF can reduce the pathological oxidative stress caused by H_2O_2 in PC_{12} cells in a dose-dependent manner by inhibiting the production of ROS and MDA and promoting the activities of SOD, CAT and GSH. This study also showed that ASF could significantly suppress the apoptosis rate of PC_{12} cells, which was increased by H2O2 exposure. In addition, ASF treatment obviously reduced the $H_2O_2^-$ induced increase in the expression levels of caspase-3 and Bax, as well as the decrease in Bcl-2 protein expression. KEGG enrichment analysis indicated that the PI3K/Akt/GSK3β/Nrf2/HO-1 pathway may be involved in the regulation of cognitive impairment by ASF (60). In the 2017 study conducted by Xing et al. (China), the role of sesquiterpene coumarin extracted from Ferula stinkingness as an inhibitor of neuroinflammation was investigated. In this study sixteen bioactive terpene coumarins were identified in the active extract of Ferula stinkingness. In addition, the anti-neuroinflammatory activities in BV-2 microglial cells were evaluated by monitoring LPS-induced nitric oxide production. The results suggest that the major compound chlorine may be responsible for the anti-neuroinflammatory effect of Awei (Ferula stinkingness). In addition, this study showed that the primary mechanism of this compound is the inhibition of mRNA expression of the inflammatory cytokines nitric oxide, tumor necrosis factor-α, cyclooxygenase-2, interleukin-6 and interleukin-1β (61). In a 2011 study by Patitucci et al. (Italy) the protection of curcumin against NMDA-induced toxicity was investigated for a possible role of the NR2A subunit. In this study, curcumin protected retinal and hippocampal neurons from NMDA-induced cell death in a dose- and time-dependent manner, confirming its anti-excitatory properties (62). In primary retinal cultures, patch-clamp experiments, consistent with the observed reduction in NMDA-induced (Ca2+)i increase, showed that a higher percentage of retinal neurons responded to NMDA with low-amplitude currents after curcumin treatment. In parallel, curcumin increased the level of NMDAr subunit type 2A (NR2A), with kinetics related to the time course of neuroprotection and decreased $(Ca^{2+})i$. It needs protein. Electrophysiology confirmed the increased activity of NR2A-containing NMdar at the plasma membrane surface. These results confirm the neuroprotective effect of curcumin against NMDA toxicity, which may be related to the increase in NR_2A levels, and encourage further studies on the possible therapeutic use of curcumin based on neuromodulation of NMDARS (63). In the study conducted by Najafifard et al. 2012 (Iran), the effect of coumarin on memory recall, tissue index and gene expression of GABAA receptors in the hippocampus of gonadectomized male rats was investigated. The results of the present study showed that the gonadectomy group had a lower initial delay in entering the dark room in the shuttle box behavioral test than the healthy group in the memory recall test. In addition, a significant decrease in the number of healthy pyramidal neurons in the hippocampus was observed, but there was no significant difference in GABAA gene expression. From the results, in the gonadectomy groups treated with different doses of coumarin, compared with the gonadectomy groups that received solvents , the amount of STL and the number of healthy pyramidal neurons decreased significantly in the memory test, but the expression of the GABAA-α2 gene increased significantly. The results of this study show that gonadectomy causes memory loss and coumarin affects memory loss by increasing the expression of the GABAA-α2 gene and decreasing the number of healthy hippocampal neurons (64). In a 2008 study by Hornick et al (Australia), the effects of the coumarin scopoletin on learning and memory on the release of acetylcholine from the synaptosomes of the brain and on long-term potentiation in the hippocampus were investigated. Scopoletin reversed the scopolamine-induced impairment in the T-maze and object recognition, while it was ineffective in normal rats. Scopoletin increased the release of 15 mM K+-induced ACh from synaptosomes and showed a bell-shaped dose-effect curve similar to that of galantamine. The effect of both compounds was blocked by the nAChR antagonist mecamylamine, indicating the involvement of nAChRs. In superfused slices from the rat hippocampus, scopoletin had no effect on basal fEPSPs, but enhanced the increase in LTP induced by fEPSPs. The effect of scopoletin on neuronal plasticity was abolished by mecamylamine. These properties of scopoletin were also observed for the positive control compound nicotine. In this study, the effects of scopoletin on the performance of mice in learning tasks and on the LTP of the hippocampus show that this compound has cognitive enhancing properties. The inhibition of LTP potentiation and presynaptic synaptosomal ACh release by mecamylamine indicates the involvement of nAChRs (65).

6. Review of behavioral tests

6.1. Passive avoidance learning behavior test:

In the passive avoidance behavior test, the shuttle box device was used to test passive avoidance memory. This device comprises two chambers, one dark and one light, whose bottoms are covered with steel wires with a diameter of 1-2 mm and a distance of one centimeter. In the shuttle box device, a mild electric shock current of 75 V, 0.3 mA was applied to the dark chamber for 3 seconds and applied only once to the soles of the animals'feet. The two chambers of this device are separated by a guillotine door. During the learning phase, the rat was placed in a lighted room with its back to the guillotine door, and the guillotine door was lifted. After the mouse entered the dark room, the door was closed and an electric shock (75 V, 0.3 mA, 50 Hz) was applied to the animal's foot for 3 seconds via metal rods embedded in the floor of the dark room. The animals were then removed from the dark room and placed in the cage. For this purpose, one of the boxes was black and completely dark, and, a 40-watt lamp was lit above the other box. The experiment was conducted in a dark room, and different training levels were performed for each rat at a specific time (66,68).

6.2. Training steps

Passive avoidance behavior was investigated based on the rats' natural preference for dark environments. The animals were trained in the following steps (69).

6.2.1. Acclimatization:

On the first day of each mouse, the animal was placed in the light chamber with the door open between the light and dark chambers and allowed to familiarize itself with the apparatus for 10 min and find the connection between the light and dark chambers through the flap. The mouse was then removed from the device and placed in an individual cage.

6.2.2. Training or learning phase:

24 hours after the adaptation phase, each mouse was placed in a light chamber. 10 seconds later, the guillotine door opened. After the mouse entered the dark room, the delay time until entering the dark room was recorded, the door was immediately closed and an electric shock was administered to the feet using the metal rods. After 20 seconds, the mouse left the chamber, and if the mouse did not enter the dark room within 300 seconds, it was removed from the experiment.

6.2.3. Reminder phase:

24 hours after the training phase, each mouse was placed in a light chamber as in the training phase, but without shock, while the guillotine door was closed. 10 seconds later, the guillotine door was opened and the time delay for entering the dark chamber was recorded. The maximum time for entering the dark room was 300 seconds. In addition, the duration of the return of the mice from the dark to the light box was recorded (70).

7. Discussion

In a 2015 study by Bagheri et al. in which memory impairment caused by D-galactose and NaNO2 was investigated by active and passive avoidance tests in mice, it was found that the Anghuzeh plant can lead to improvement in amnesia. However, the mechanism of cation of this plant was not investigated in this study (71). In 2012, Vijayalakshmi et al. investigated the effect of watercress on memory and learning using the plus maze and passive avoidance test. The results of their studies showed that the aqueous extract of F assa-foetida can improve learning and memory compared to normal animals. In this study, these positive effects of the aqueous extract of F assa-foetida were attributed to the facilitation of cholinergic transmission due to the inhibition of acetylcholinesterase (AchE) and to some extent to the enhancement of the effect on the internal antioxidant system (72). In addition, electrophysiological findings in the CA1 region of the hippocampus showed a significant deficit in LTP after scopolamine injection, which is consistent with previous studies (73). In this study, an increase in LTP induction was observed after injection of donepezil and gumosin20 in both Sco+DP and Sco+Gum20 groups. The administration of gumosin10 in the Sco+Gum10 group led to a relative improvement, so that there was no difference to the scopolamine group or the control group. The improvement in LTP may be caused by changes in the function and structure of presynaptic or postsynaptic neurons, or both. Considering that structural changes require more time, the observed recovery seems to be due to the improvement in the function of presynaptic or postsynaptic neurons. To investigate the molecular mechanisms, the expression of various genes was therefore examined using RT-PCR. In this study, it was observed that the level of CREB in the scopolamine group was significantly reduced, and the

injection of Donepezil and two doses of Gummosin caused a relative increase and return of this factor to normal levels. In line with these results, studies have shown that CREB is reduced in the hippocampus of Alzheimer's mice, which is associated with synaptic plasticity and memory deficits. In addition, studies have shown that CREB plays an important role in neuronal plasticity, cell survival, neurogenesis and cognition in the hippocampus and cortex. Studies have shown that learning and memory are related to glutamatergic transmission and involve NMDA receptors in the CNS. Increased activation of the NMDA receptor signaling pathway leads to facilitation of learning and memory (73). As explained in the introduction, NR2 receptors cause damage when they are located outside the synapse, especially the NR2B type, whereas NR2 receptors located inside the synapses, mostly the NR2A type, have neuroprotective effects. NR2B levels increase in Alzheimer's disease models (74). In one study, excessive activation of the NR2B receptor was shown to lead to memory and learning deficits in rats in the MCAO model, and its inhibition can be considered as a therapeutic target in Alzheimer's and dementia patients. Therefore, in this study, the expression of NR2B and NR2A genes was investigated using real-time PCR technique. This study found that, consistent with previous studies, NR2A gene expression decreased in the scopolamine group. Administration of donepezil resulted in a significant increase in the expression of this gene compared to the scopolamine group, while injection of gummosin10 and gummosin20 relatively increased the expression of the NR2A gene. In addition, scopolamine increased the expression of NR2B in our study, but treatment with donepezil and gummosin20 had the same effect in returning the expression of NR2B to control levels, while injection of gummosin10 showed a relative improvement. As described, stimulation of intrasynaptic NMDA receptors activates neuronal survival signaling pathways, while activation of extra-synaptic NMDA receptors activates cell death pathways. Stimulation of NR2A receptors leads to activation of the PI3k/Akt signaling pathway, increase in CREB gene expression and suppression of genes related to cell death, ultimately leading to neuronal survival. Once NR2A receptors are open, PI3K, activated by Ca^{2+} and calmodulin, phosphorylates the membrane phospholipid PtdIns P_2 to PtdIns P_3. Subsequently, PtdIns P_3 reacts with PDK1 kinase, enters the membrane and activates AKt by phosphorylation. Akt promotes neuronal survival by phosphorylating downstream factors. In addition, activation of NR2A receptors increases the expression of genes related to neuronal survival. NR2A activity and calcium influx activate the Ras/ERK signaling pathway, which then activates CREB nuclear CAMKs. Activation of CREB leads to increased expression of genes related to neuronal survival and protects neurons from apoptotic effects (75). As mentioned above, NR2B receptor activity is associated with cell death. NR2B receptors attenuate the activity of NR2A receptors. For example, when NR2B receptors are activated, CREB is inactivated, which inactivates the ERK signaling pathway with the inactivation of CREB, preventing the activation of CREB and increasing the expression of genes related to cell death (Figure 4) (76). Therefore, antagonists of NR2B receptors can be considered as a therapeutic target in many pathological conditions of neurodegeneration such as ischemia and dementia. Considering that in our study gummosin20 significantly and gummosin10 relatively increased the expression of NR2A and CREB gene and decreased the expression of NR_2B gene, it is possible that gummosin leads to an increase in neuronal survival and an improvement in memory and learning in a dose-dependent manner through the activation of NR_2A/CREB receptor. On the other hand, in 2014, Bunk et al. used Ifenprodil to block the NR_2B subunit of the NMDA receptor, and in this study, blocking this receptor was found to significantly increase, internal neurogenesis (77,78). According to this study, the NR_2B subunit of the NMDA receptor has a negative regulatory role in internal neurogenesis. Therefore, considering that gummosin led to a significant decrease in NR2B subunit expression in our study, it is possible that this agent stimulates internal neurogenesis and thereby improves memory and synaptic plasticity. To further investigate the possible mechanism of memory improvement, we examined the number of neurons in the hippocampus region using the stereology technique. The stereological results of our study showed that the administration of scopolamine leads to significant structural changes in the CA_1 and CA_3 regions (78). These changes include a decrease in the number of neurons and glial cells. These results are consistent with previous studies that have shown that scopolamine leads to structural changes in the hippocampus region of the brain and subsequent neurobehavioral functions (76).

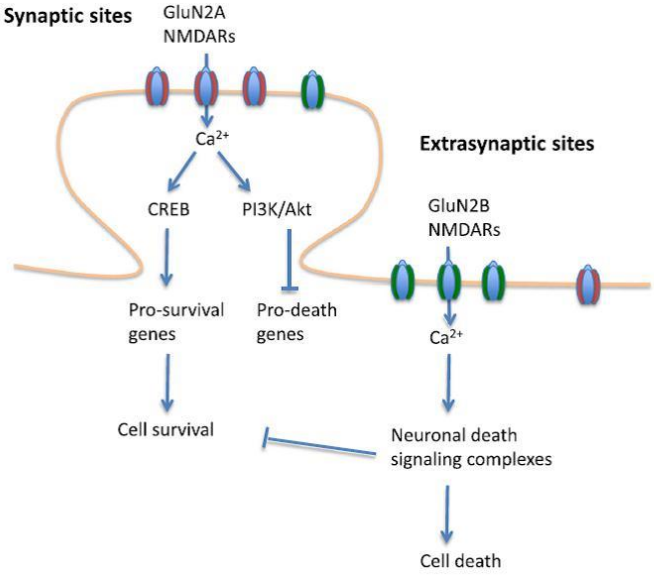

Figure 4. Signaling pathway of NMDA receptors function

4. Discussion

Learning is undoubtedly one of the most important psychological processes. Learning is the basis for everything that distinguishes humans from other humans and animals. Learning can be defined as a change in behavior based on experience, and memory corresponds to the storage of these experiences. It is obvious that these two phenomena are interdependent and should be studied together. Knowledge of learning methods not only contributes to the understanding of normal behavior, but also offers the possibility of understanding the conditions that cause abnormal behavior to occur. There are several theories that examine the learning process and the factors that influence it. Almost a hundred years ago, the subject of learning was dominated by philosophical theories such as the philosophy of Aristotle and Plato. With the first experimental studies by Ebbinghaus, Pavlov and Trendike, experimental research methods were established, and based on the numerous scientific documents from research laboratories around the world, more comprehensive theories and more precise principles on learning were established. According to the definition of learning, which is seen as more or less permanent change in behavior as a result of experience, we can imagine that we are confronted with all kinds of learning in life. Since behaviors take different forms, there are also different types of learning. Psychologists believe that learning occurs when the organism is exposed to certain types of sensory experiences. The learning process is usually divided into social or observational learning and non-social or individual learning. Social learning is learning that is formed as a result of exposure to non-sensory experiences, and non-social learning is a motor response due to a sensory response, which includes simple learning, dependent learning and complex learning.

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Authors' Contribution

Concept and design of the study: Hossein Amini-Khoei, Atefeh Asadi-Rizi
Data collection: Atefeh Asadi-Rizi
Analysis and interpretation of the data: Mehrdad Shahrani.
Drafting of the manuscript: Atefeh Asadi-Rizi
Critical revision of the manuscript with regard to important intellectual aspects: Leila Amjad, Atefeh Asadi-Rizi
Statistical analysis: Mehrdad Shahrani, Atefeh Asadi-Rizi
Administrative, technical, and material support: Atefeh Asadi-Rizi

Ethics

The present study was approved by the Ethics Committee of Falavarjan Branch University, Islamic Azad University, Isfahan, Iran

Conflict of Interest

The authors declare that they have no conflict of interest.

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