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Therapeutic and medicinal effects of snowdrop (*Galanthus* spp.) in Alzheimer's disease: A review

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Abstract:

Genus *Galanthus* (Amaryllidaceae) is an early spring flowering bulbous plant. *Galanthus* species contain alkaloids that have shown pharmacological activity. Galanthamine is an alkaloid that was extracted from *Galanthus* and other Amaryllidaceae. Owing to its acetylcholinesterase (AChE) inhibitory activity, galanthamine is used and marketed to treat Alzheimer's disease (AD). The aim of the present study, while introducing the botanical and pharmacological characteristics and various aspects of the medicinal plant *Galanthus*, is to emphasize the effect of this plant in the treatment of AD. In this web-based study in 2021, articles indexed in scientific databases in English language, including ISI Web of Knowledge, PubMed, Scopus, MedLib, Medknow, SID, ISC, and also articles and e-books published in Springer, Elsevier, John Wiley and Sons, and Taylor and Francis were evaluated from 1990 to 2021, using the following keywords: "*Galanthus*" "galanthamine," "Alzheimer's disease." Amaryllidaceae-type alkaloids possess an anticholinesterase activity. The most studied *Galanthus* alkaloid, galanthamine, is a long-acting, selective, reversible, competitive inhibitor of AChE and an allosteric modulator of the neuronal nicotinic receptor for acetylcholine (ACh). Owing to its AChE inhibitory activity, galanthamine is used to treat certain stages of AD. Galantamine can act as a parasympathomimetic agent, especially as a reversible cholinesterase inhibitor. Galantamine is not structurally associated with other AChE inhibitors. Hence, its proposed mechanism of action involves the reversible inhibition of AChE, preventing hydrolysis of ACh that results in an increased concentration of ACh at cholinergic synapses.

Keywords:

Acetylcholine, alkaloid, Alzheimer, galanthamine, *Galanthus*

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Introduction

The Amaryllidaceae family has about 85 genera and more than 1100 species spread worldwide, especially in the tropics.[1] This family is one of the 20 most important plant families containing alkaloid compounds.[2] Snowdrop (*Galanthus* spp.) is a perennial bulbous plant related to this family.[3] The unique diversity of alkaloids in this genus has been revealed by phytochemical research. Many of them have been reported for the first time, and their biological activity is still unknown. Galantamine is one of these compounds, mainly found in the *Galanthus* and other Amaryllidaceae plants.[4] Galantamine was first isolated in 1952 from Caucasian snowdrop (*Galanthus woronowii*),[5] native to the Caucasus Mountains in Russia and eastern Turkey and Iran. It was then extracted from the *Galanthus nivalis*,[6] native to the Mediterranean coast and the northern temperate regions. Today, galantamine is obtained from Summer snowflake (*Leucojum aestivum*), commonly found in Europe and North America.[7] This alkaloid has been used to treat Alzheimer's disease (AD) since 2011. AD was first described by the German psychiatrist Alois Alzheimer in 1907.[8] The disease was prevalent in the first decades of the twentieth century, but

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dementia (cognitive impairment) is expected in the elderly today. The American Alzheimer's Association estimates that approximately 5.2 million Americans currently suffer from AD.[9] This disease is the most common cause of cognitive impairment in the elderly according to the Alzheimer's Association. It means that two-thirds of the causes of cognitive impairment are related to AD.[10] This disease is associated with cognitive disorders, such as impaired memory, perception, and a disruption in daily activities and social relations.[11] It is not easy to determine the cause of any cognitive impairment because accurate diagnosis is not possible in lifetime.[10]

AD is a degenerative neurological, progressive, and fatal disorder characterized by degeneration of the cerebral cortex and loss of nerves under the influence of acetylcholine (ACh) (cholinergic) in the anterior part of the brain.[12] Preliminary strategies in the treatment of AD focus on the cholinergic system because one of the pathological events in AD is the degeneration of cholinergic neurons in the underlying structures of the frontal lobe. The oldest hypothesis, still based on pharmacological therapies, is the cholinergic hypothesis, which relates to a defect in neurotransmission because of low ACh production. Various strategies have been studied, including cholinesterase inhibitors, choline precursors, and postsynaptic and presynaptic stimulation with muscarinic and nicotinic agonist.[13] One of the first drugs approved for treating AD, acetylcholinesterase (AChE) inhibitors, is the enzyme responsible for hydrolyzing ACh. The AChE inhibitor increases ACh levels, followed by neurotransmission. AD treatment has so far been based on three FDA-approved cholinesterase inhibitors, including galantamine, rivastigmine, and dopenzil [Figure 1], as well as the *N*-methyl-D-aspartate receptor antagonist memantine, which is used to treat joints and in severe stage of AD.[14] However, these drugs have only a sedative and symptomatic pharmacological effect, and with continued use, their impact is reduced and eventually eliminated.[15,16] Natural products, especially plant alkaloids, are considered as a source of medicinal compounds. Alkaloids are a particular group of low molecular weight nitrogenous compounds that act at different cellular levels within organisms. They are involved in the biological processes of plants, animals, and microorganisms that live in different environments. These compounds are found in approximately 25% of higher plant species, especially in Apocynaceae, Asteraceae, Fabaceae, Papaveraceae, Rubiaceae, and Solanaceae.[17-19]

Galantamine, an alkaloid of the genus *Galanthus*, plays a dual role in the cholinergic system; it acts as a selective AChE inhibitor and an allosteric agonist of nicotinic acetylcholine receptors (nAChR).[20,21] This study was aimed to introduce the botanical, pharmacological characteristics, and various aspects of the medicinal plant *Galanthus*, emphasizing the effect of treating AD.

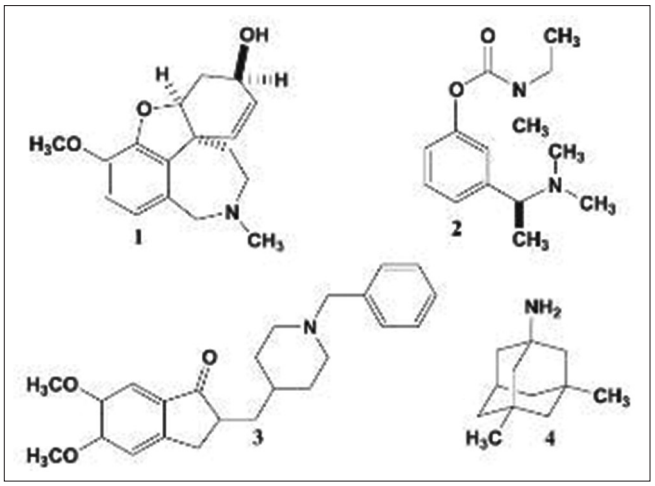

Figure 1: Drugs currently in use for the treatment of Alzheimer's disease; (1) Galanthamine, (2) rivastigmine, (3) donepezil, and (4): *N*-methyl-D-aspartate receptor antagonist memantine[28]

Materials and Methods

In this web-based study, the search process on the published articles evaluating medicinal effects of snowdrop (*Galanthus* spp.) in AD was conducted. Articles indexed in scientific databases including ISI Web of Knowledge, PubMed, Scopus, MedLib, SID, ISC, and also articles and e-books published in Springer, Elsevier, John Wiley and Sons, and Taylor and Francis were evaluated from 1990 to 2021, using the following keywords: "Galanthus" "galanthamine," "Alzheimer's disease."

Geographical distribution of *Galanthus*

The *Galanthus* is distributed in Europe, Asia Minor, and the Caucasus region. Its distribution areas are the Pyrenees in the west, Caucasus and Iran in the east, and Sicily, Peloponnese, and Lebanon in the south. Because of the human intervention and agriculture, its northern distribution cannot be studied.[22] Some *Galanthus* species are widely distributed, whereas others are limited to small areas. *G. nivalis*, for example, is native to large areas of Europe that stretching from the Pyrenees to Italy, Northern Greece, Ukraine, and the European regions of Turkey. However, *G. trojanus* is a rare plant found exclusively in less than 10 km^2 in western Turkey.[23] Most species of this plant (14 species) are collected in Turkey.[24,25]

AD

AD is an irreversible, progressive neurodegenerative disorder associated with the gradual decline of memory, cognition, speech, language, visual-spatial perception,

behavior, and daily activities, leading to complete cognitive impairment and death. AD symptoms include extracellular nerve plaques in old age and intracellular neurofibrillary tangles (NFT). There is also synaptic disruption and neuronal function, a decrease in the dendritic shape of the dendrites, and a reduction in the number of neurotransmitters, leading to progressive loss of neurons and brain volume.[19,26,27] A comparison of these features in healthy and diseased brains with advanced Alzheimer's is shown in Figure 2.

Cholinergic neurotransmission in the central nervous system

Transmission of information between cholinergic neurons [Figure 3] occurs by presynaptic neurons in the synaptic cleft through ACh release. ACh is released in the postsynaptic nerves to bind to nAChR [Figure 4]. Most released ACh (about 90%) is rapidly hydrolyzed to choline and acetate by AChE, which is found in soluble form in the synaptic cleft or bound with the basement membrane. The remaining ACh (about 10%) is released through the synaptic cleft and reaches the postsynaptic neuron to interact with and activate cholinergic receptors. ACh rapidly hydrolyzed by AChE after separation from the receptors.[28,29]

Defects in cholinergic neurotransmission in AD

Major pathological features of AD are directly related to neurodegeneration. Inside a neuron is shown in Figure 4, in which NFTs containing hyperphosphorylated tau protein are formed. This condition directly affects the storage, vesicle maturation, and release of neurotransmitters. Abnormal deposition of Aβ extracellularly causes insoluble fibrillar accumulations (plaque Aβ) [Figure 5]. This condition causes cascading events that begin with neuronal damage and lead to death.[28]

Alkaloids as potential multifunctional drugs for the treatment of AD

Herbal medicine is one of the oldest treatments identified by man. The use of medicinal plants has long attracted the attention of medical professionals for the prevention and treatment of diseases.[30] Alkaloids are natural organic compounds that contain nitrogen found in plants. They are secondary metabolites long been used by specialists and the general public for treatment. It is not surprising that more than 27,000 alkaloids have been identified so far. These compounds have diverse structures and biological functions associated with various pathologies such as AD. Two cholinesterase inhibitors approved by FDA, galantamine and rivastigmine (a synthetic derivative of physostigmine), are alkaloid compounds.[31] Many alkaloid compounds such as isoquinolines, piperidines, β-carbolines, and tetrahydroisoquinolines can act very efficiently as inhibitors of AChE and butyrylcholinesterase.[28]

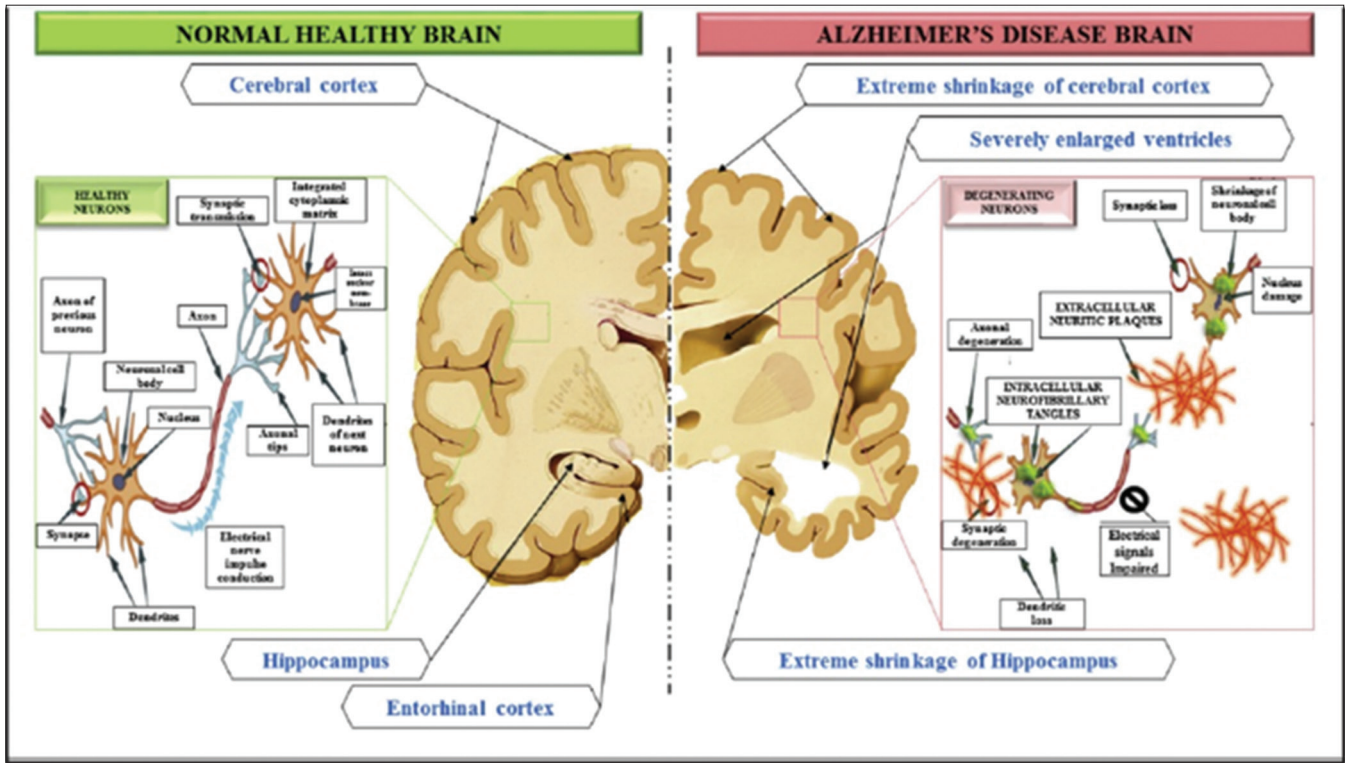

Figure 2: Schematic diagram comparing a normal healthy brain and brain at severe stage of Alzheimer's disease (AD). AD brain shows decrease in brain volume, accumulation of nerve plaque (red coloured fibrous accumulations) and neurofibrillary tangles (green colored accumulations), loss of synaptic connections, and neuronal loss[27]

Table 1: Some studies and other characteristics about the therapeutic effects of snowdrop (Galanthus spp.) and galanthamine in AD

Row	Authors (years)	Title	Findings Regarding This Study
1	Ayaz *et al*. (2019)[42]	Natural products-based drugs: potential therapeutics against AD and other neurological disorders	Galanthamine has been used as the promising drug (known as Nivalin) for the symptometric treatment of AD.
2	Lima and Hamerski (2019)[28]	Alkaloids as potential multi-target drugs to treat AD	Galanthamine has dual action on the cholinergic system, as a selective inhibitor of AChE and allosteric agonist of nAChR. Furthermore, galanthamine is able to inhibit amyloid beta aggregation and toxicity, presents neuroprotective effects, and prevents neuronal oxidative damage produced by reactive oxygen species.
3	Oka *et al*. (2016)[43]	Predicting the neural effect of switching from donepezil to galantamine based on single photon emission computed tomography findings in patients with AD	Galantamine therapy, unlike donepezil, is characterized by a dual mechanism of action that may increase acetylcholine and the nicotinic receptor-modulation effect within the frontal lobe, both of which are associated with apathy and executive dysfunction in AD patients.
4	Jiang *et al*. (2015)[44]	Efficacy and safety of galantamine treatment for patients with AD: a meta-analysis of randomized controlled trials	Galantamine significantly improves cognitive, behavioral, and global performance in patients with AD. However, it needs to be used with caution in clinical settings.
5	Hager *et al*. (2016)[45]	Effect of concomitant use of memantine on mortality and efficacy outcomes of galantamine treated patients with AD: post-hoc analysis of a randomized placebo-controlled study	Long-term treatment with galantamine significantly reduced mortality and declining cognition and daily living activities in mild to moderate AD patients.
6	Takeda *et al*. (2006)[16]	A systematic review of the clinical effectiveness of donepezil, rivastigmine, and galantamine on cognition, quality of life, and adverse events in AD	This review has demonstrated that galanthamine can delay cognitive impairment in patients with mild to moderately severe AD for at least 6 months duration.
7	Heinrich and Teoh (2004)[5]	Galanthamine from snowdrop - the development of a modern drug against AD from local Caucasian knowledge	Galanthamine provides an effective symptomatic treatment for patients with AD. At the same time, it also enables a delay in the progression of the disease.
8	Lilienfeld (2002)[36]	Galantamine - a Novel cholinergic Drug with a unique dual mode of action for the treatment of patients with AD	Galantamine is an effective treatment for AD with an excellent tolerability profile.
9	Raskind and Truyen (2002)[46]	The cognitive benefits of galantamine care sustained for at least 36 months: a long-term extension trial	Patients taking galanthamine for the entire 36-month period continued to show cognitive benefits at 36 months when compared with the expected decline of a historical placebo group.
10	Raskind *et al*. (2000)[47]	Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension	Patients who had received placebo for the first 6 months and then switched to galanthamine never achieved the level of function seen in patients treated with galanthamine throughout, emphasizing the importance of early treatment to maximize benefit.

AD=Alzheimer's disease, AChE=acetylcholinesterase, nAChR=nicotinic acetylcholine receptors

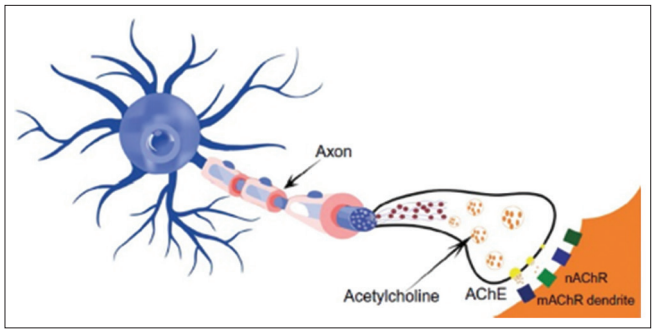

Figure 3: Representation of cholinergic neurotransmission. Acetylcholine (ACh) is synthesized in the presynaptic neuron, released in the synaptic cleft, and moves to the postsynaptic neuron where it binds to cholinergic receptors activating them. ACh is hydrolyzed by acetylcholinesterase in the synaptic cleft[19]

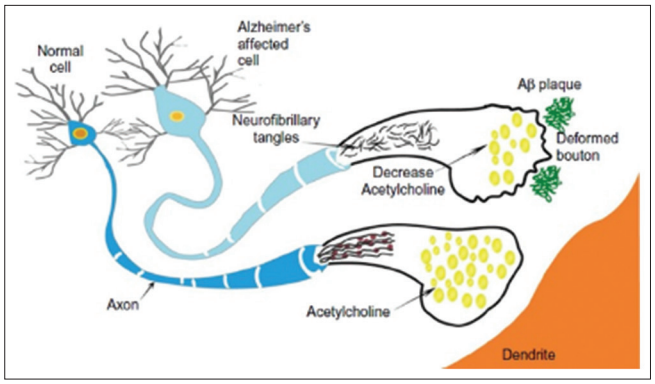

Figure 4: Representation of a healthy neuron and an Alzheimer's disease–affected neuron. In the Alzheimer's-affected neuron, we can see the intracellular formation of neurofibrillary tangles, a decrease in the number of acetylcholine vesicles, and the extracellular deposition of Aβ plaque[19]

Galantamine

Galantamine is one of the phenanthrene-derived alkaloids. It is chemically similar to morphine, and its chemical structure is shown in Figure 1 (No. 1). Its empirical formula is $C_{17}H_{21}NO_3$, and its molecular weight is 287.35 g/mol. The melting point of galantamine is 269–370°C (hydrogen bromide salt), and its solubility in water is 10 mg/ml (HBr salt). It is soluble in hot water

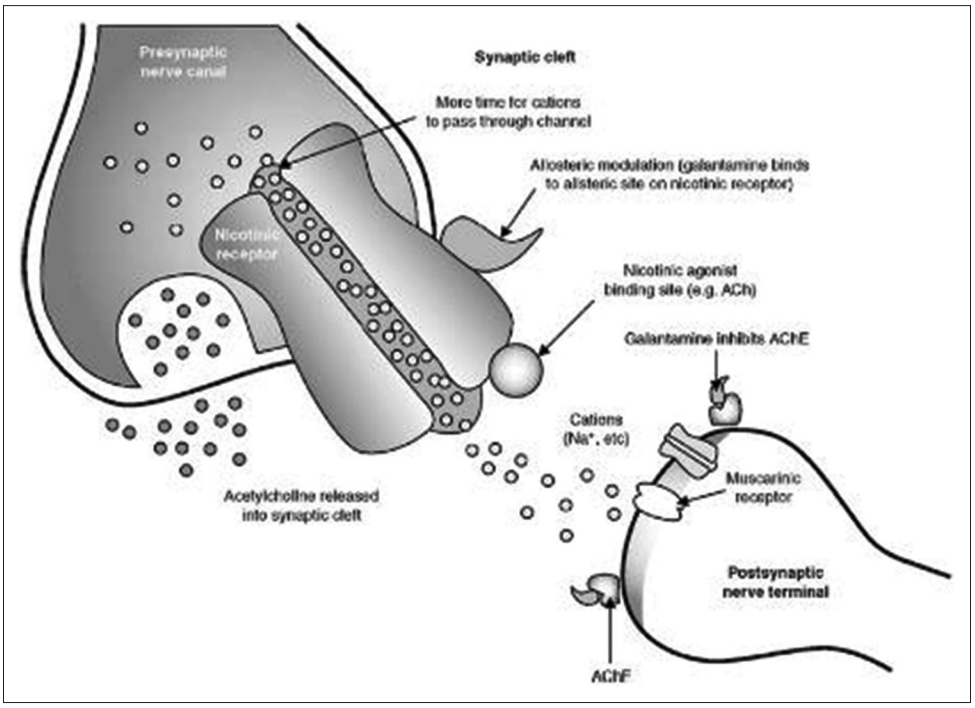

Figure 5: Proposed dual mechanism of action of galantamine: Competitive acetylcholinesterase inhibition and allosteric nicotinic modulation. Reproduced with permission from Farlow, M.R. (2003). Clinical pharmacokinetics of Galantamine. Clinical Pharmacokinetics 42(15):1383–1392. (Copyright 2003 Springer Nature)

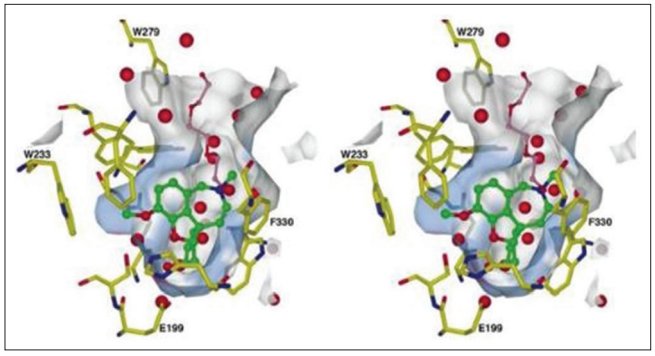

Figure 6: Stereo view of galantamine in active site gorge of Tc-AChE (Galantamine is shown in green ball-and-stick model)[39]

and soluble in alcohol, acetone, and chloroform, and less soluble in benzene and ether. The yield of galantamine from the *Leucojum aestivum* ranges from 0.1 to 2% of dry weight.[10,32-34]

Mechanism of action of galantamine

Galantamine is not structurally similar to other AChE inhibitors. However, the proposed mechanism of action includes its reversible inhibitory effect on AChE. As a result, the hydrolysis of acetylcholine is inhibited, and the concentration of ACh in the cholinergic synapses increases.[35] Galantamine binds to nAChRs in allosteric way and possibly acts as an agonist for acetylcholine in these receptors [Figure 5].[36] In active site of AChE, there is a catalytic triple set (Ser-200, His-440, and Glu-327) situated at the bottom of a deep and narrow gorge creased with aromatic residues. There is a subsite with Trp-84 next to the depth of the above-mentioned cavity. Trp-84 acts as a binding site for decamethonium, ACh, and edrophonium. The Trp-279 is also located at the peripheral site at the opening of the gorge, which is responsible for binding of second quaternary group of decamethonium. The distance between Trp-84 and Trp-279 is 12 Å.[37-39] Galantamine binds at the base of the active site gorge of Tc-AChE; Therefore, it will interact with the acyl-binding pocket and the indole ring of Trp-84 [Figure 6]. The third group of amine galantamine has no interaction with Trp-84. It was detected a π–π interaction between the double bond of cyclohexene ring, as an alternative.[40,41] Some studies and other characteristics about the therapeutic effects of snowdrop (*Galanthus* spp.) and Galanthamine in AD are summarized in Table 1.

Conclusion

A review of the articles indicates that the Amaryllidaceae family alkaloids generally have antiviral and antitumor properties and act as anticholinesterases. From this family, *Galanthus* genus is a rich source of new compounds. Galantamine is the most widely studied compound in the field. It is commonly used in medicine as a potent reversible inhibitor of AChE to treat AD, polio, and other neurological diseases. Galantamine is not structurally similar to other AChE inhibitors. The proposed mechanism of action involves its reversible inhibitory effect on AChE, which inhibits the hydrolysis of acetylcholine and ultimately increases

the concentration of ACh at cholinergic synapses. Galantamine also binds to nAChRs in an allosteric way and acts as an acetylcholine antagonist in these receptors.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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