Naturally Occurring Chemicals Against Alzheimer's Disease

Edited by
Tarun Belwal | Seyed Mohammad Nabavi
Seyed Fazel Nabavi | Ahmad Reza Dehpour
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Contents

Chapter 3
Phytochemicals/plant extract against Alzheimer's

Section 3.1
Phytochemicals (pure compounds)

3.1.4. Galantamine

Vaibhav Rathi

3.1.5. Rivastigmine

Shahira M. Ezzat, Mohamed A. Salem, Nihal M. El Mahdy and Mai F. Ragab

3.1.6. Quercetin

Fatma Tugce Guragac Dereli and Tarun Belwal

3.1.7. Valerenic and acetoxyvalerenic acid

Sarita Khatkar, Amit Lather and Anurag Khatkar

3.1.8. Huperzine A

Weaam Ebrahim, Ferhat Can Özkaya and Galal T. Maatooq

3.1.9. Caprylic/capric triglyceride

Manjul Mungali, Navneet Sharma and Gauri

3.1.10. Berberine

Merve Keskin, Gülsen Kaya, Fatma Tugce Guragac Dereli and Tarun Belwal

3.1.11. Hypericin and pseudohypericin

Koula Doukani, Ammar Sidi Mohammed Selles and Hasna Bouhenni

3.1.12. Protopine

Bijo Mathew, Della G.T. Parambi, Manjinder Singh, Omnia M. Hendawy, Mohammad M Al-Sanea and Rania B. Bakr

3.2.2. *Panax ginseng* c.a. Meyer

Amit Bahukhandi, Shashi Upadhyay and Kapil Bisht

3.2.3. *Melissa officinalis* (lemon balm)

Koula Doukani, Ammar Sidi Mohammed Selles and Hasna Bouhenni

3.2.4. *Bacopa monnieri* (Brahmi)

Tanuj Joshi, Abhishek Gupta, Prashant Kumar, Anita Singh and Aadesh Kumar

3.2.5 *Centella asiatica*

3.2.6. *Rosmarinus officinalis* L.

3.2.7 *Valeriana officinalis* (valerian)

3.2.8. *Matricaria recutita*

Fatma Tugce Guragac Dereli and Tarun Belwal

3.2.9. *Galanthus nivalis* L. (snowdrop)

Devesh Tewari, Tanuj Joshi and Archana N. Sah

3.2.10. Guggulu [*Commiphora wightii* (Arn.) Bhandari.]

Jyoti Upadhyay, Sumit Durgapal, Arvind Jantwal, Aadesh Kumar, Mahendra Rana and Nidhi Tiwari

3.2.19. *Convolvulus prostratus*

Deepak Kumar Semwal, Ankit Kumar, Ruchi Badoni Semwal and Harish Chandra Andola

3.2.20. *Celastrus paniculatus*

Harikesh Maurya, Rajewshwar K.K. Arya, Tarun Belwal, Mahendra Rana and Aadesh Kumar

3.2.21. *Uncaria rhynchophylla* (Miq.) Jacks

Devina Lobine and Mohamad Fawzi Mahomoodally

3.2.22. *Alpinia officinarum*

Arpan Mukherjee, Gowardhan Kumar Chouhan, Saurabh Singh, Koustav Chatterjee, Akhilesh Kumar, Anand Kumar Gaurav, Durgesh Kumar Jaiswal and Jay Prakash Verma

3.2.23. *Himatanthus lancifolius* (Müll.Arg.) Woodson

Devina Lobine and Mohamad Fawzi Mahomoodally

3.2.24. *Nelumbo nucifera*

Firoz Akhter, Asma Akhter, Victor W. Day, Erika D. Nolte, Suman Bhattacharya and Mohd Saeed

3.2.25. *Zingiber officinale*

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He obtained his undergraduate degree in pharmaceutical science and a master's degree in biotechnology before receiving a Ph.D. from India. Before his move to Zhejiang University, he worked on using natural products as nutraceutical agents, examining their functional activities (animal model), and developing in vitro cell culture and advanced extraction techniques. For his exemplary work, the Indian government awarded him the prestigious Governor Award for Best Research for 2 consecutive years (2016 and 2017). He has successfully completed a project as principle investigator (2018−20), funded by the China Postdoctoral Science Foundation. His excellent research credentials are reflected by more than 60 peer-reviewed scientific publications and eight book chapters with over 800 citations. He is currently engaged in editing six scientific books and three special issues as guest editor. Moreover, he is serving as an associate editorial board member of *Mini-Reviews in Medicinal Chemistry* and *Current Pharmaceutical Biotechnology.* He is an active member of the European Society of Sonochemistry and was also an invited speaker at the Fourth International Symposium on Phytochemicals in Medicine and Food (Xi'an, China, Nov. 30 to Dec. 4, 2020). In addition, he is an active reviewer of several prestigious journals.

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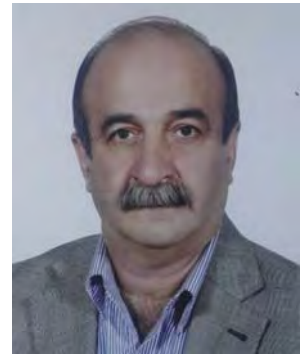
Ahmad-Reza Dehpour



Ahmad-Reza Dehpour is an Iranian pharmacologist and biomedical scientist, among the top 1% in the world, and one of the world's highly cited researchers announced by Thomson Reuters ISI. He is currently a distinguished professor of pharmacology at the School of Medicine, Tehran University of Medical Sciences.

He was born in Siahkal, Gilan province, north of Iran, in 1948. He earned his doctorate in pharmacy from Tehran University in 1972. He earned a Ph.D. in pharmacology from the Medical School of Tehran University under the supervision of Professor Frank Michal, who was a guest professor from Cambridge University living in Iran at that time. His thesis title was *Some Biophysical and Biochemical Aspects of Blood Cell Membranes*.

He began his academic career by joining Tehran University of Medical Sciences as an assistant professor of pharmacology in 1978. He was promoted to associate professor of pharmacology in 1983 and consequently to professor of pharmacology in 1993 and was awarded a distinguished professorship in 2011. He has devoted himself to teaching fundamental concepts in pharmacology to undergraduate and graduate students, also serving as an undergraduate and graduate research mentor and advisor. In addition, he was a visiting professor at the Swiss Federal Institute of Technology, Zurich from 1998 to 1999.

In addition to his academic contributions, he was general secretary of the Iranian Society of Physiology and Pharmacology from 1981 to 1986. He became a member of the Iranian Board of Pharmacology in 1999 and has been a member of the Iranian Academy of Medical Sciences since 2007. He was president of the Iranian Society of Physiology and Pharmacology from 2005 to 2007. He is also an adjunct professor at the Institute of Biochemistry and Biophysics, University of Tehran.

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Chapter 3.1.4

Galantamine

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Introduction

Galantamine is a selective competitive and reversible Ach inhibitor alkaloid derived from various plant sources, while in vitro production is also only carried out via plant parts. It has been used and studied extensively for many years for various uses, previously being a drug of choice for myasthenia gravis, but as there are many other Ach inhibitors it also has shown excellent potential in the treatment of Alzheimer's disease with minimal side effects—the side effects are usually mild and the discontinuation rate is also low as compared to other Ach inhibitors. This chapter compiles the data from various research and peer reviews regarding the use of galantamine in Alzheimer disease.

Galantamine is found in various plant sources, mainly from the genera *Amaryllis*, *Lycoris*, *Hippeastrum*, *Ungernia*, *Leucojum*, *Zephyranthes*, *Narcissus*, *Galanthus*, *Hymenocallis*, and *Haemanthus* and is a naturally occurring alkaloid of the family Amaryllidaceae, which is a selective competitive and reversible acetylcholinesterase (Ach) inhibitor, which can also be prepared synthetically by various methods. Galantamine is used in various neurodegenerative diseases, especially dementia and Alzheimer's disease which is the main cause of dementia (around 75%) worldwide. Galantamine is prescribed to treat mild-to-moderate Alzheimer's disease. It has relatively few adverse effects and is considered relatively safer to use as compared to tacrine, which was withdrawn due to its severe side effects. Galantamine is sold as galantamine hydrobromide salt as Razadine or Reminyl, and galantamine hydrobromide is also used for the treatment of other neurological diseases such as poliomyelitis (Emilien et al., 2004; Marco-Contelles et al., 2006; Coelho dos Santos et al., 2018; Viegas et al., 2005; Heinrich and Teoh, 2004; Cherkasov, 1978).

This chapter discusses the biological and geographical distribution, various sources from which galantamine is obtained, and the chemistry, pharmacology, and Alzheimer disease clinical study profiles of galantamine.

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Biological and geographical distribution

Galantamine can be extracted from various genera of plants, namely *Amaryllis*, *Lycoris*, *Hymenocallis*, *Ungernia*, *Hippeastrum*, *Leucojum*, *Narcissus*, *Galanthus*, *Zephyranthes*, and *Haemanthus* and it can also be prepared synthetically using various methods (Cherkasov, 1978; Cherkasov and Tokachev, 2002).

Biological sources

1. *Leucojum aestivum* L. (snowflake)—This is found in the Mediterranean region and eastern Europe with a yield range from 0.1% to 0.3% (Stefanov, 1990)
2. *Narcissus* species—the bulbs of *Narcissus* plant are utilized for the extraction of galantamine, around 0.1% yield is found in the plant, some good plants of this genus include *N. pseudonarcissus* which gives a relatively high yield (0.13%) (Cherkasov and Tokachev, 2002; Kreh, 2002)
3. *Ungernia victoris—Ungernia victoris* Vved is found in Tajikistan and Uzbekistan is perennial species. Total alkaloid in leaves and bulbs is about 0.27%−0.0.71% and 1.18%−1.65% respectively. (Sadykov and Khodzimatov, 1988)
4. *Lycoris radiata—Lycoris radiata* Grey is a plant which is widespread in China, Korea and Japan. The *L. radiata* exact yield was not reported by the authors (Hayashi et al., 2005).

In vitro production of galantamine

Narcissus confusus and *Narcissus aestivum* are the only two species used for in vitro production of galantamine, the in vitro production was done using callus culture and micropropagation. Twelve μg/g from *L. aestivum* and 0.03 μg/g dry weight yield from *L. confusus* was obtained from the callus culture (Pavlov et al., 2007; Proskurina; Yakovleva, 1955).

Chemistry

Galantamine, also known as galanthamaine, is (1S,12S,14R)-9-methoxy-4methyl-11-oxa-4-azatetracycloheptadeca-6(17),7,9,15-tetreb-14-ol, and is an alkaloid found in different plants of the family Amaryllidaceae, some examples of which include *Narcissus pseudonarcissus* (daffodil) and *Leucojum aestivum* (snowflake).The chemical structure of galantamine is given in Fig. 3.1.4.1 (Attar-ur-Rahman, 2019; Thomas et al., 2008; Zohra and Uriel, 2005):

Pharmacology

Galantamine is reported to have a distinctive dual mode of action, which includes reversible and competitive inhibition of AChE, along with positive modulation of nAChRs (Albuquerque et al., 2001).

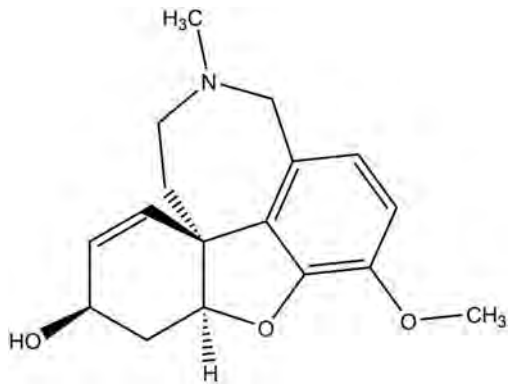

FIGURE 3.1.4.1 Chemical structure of galantamine.

AChE inhibition: Cholinergic neuron reduction has been correlated with cognitive deficits in AD, which affects learning and memory, in turn reducing the breakdown of Ach. Galantamine inhibits the interruption and breaking of Ach by binding to the active site of AChe competitively and reversibly (Albuquerque et al., 2001; Thomsen et al., 1990).

The two areas most affected in AD patients are the hippocampus and frontal cortex of the brain, where galantamine binds, and inhibit transmission by binding to AChE receptors (Thomsen et al., 1991).

nAChR modulation: the drop in the numbers of nAChR receptors plays a major role in AD. Many types of nAChR protein subunits are known, nine types of α-subunits are found in the brain, on which Ach binds, and three types of β-subunits are known, which are basically structural subunits. Loss of nAChRs is seen in the hippocampus and neocortex area of the brain in cases of AD. Galantamine binds to nAChRs at a secondary binding site on the α7 subunit, although galantamine cannot activate the site itself, rather it behaves like an allosteric modulator; when ACh and galantamine bind together on their respective site on nAChRs, galantamine starts a cellular response which is induced by ACh. Galantamine actually makes nAChRs more sensitive to ACh (Albuquerque et al., 2001; Martin-Ruiz et al., 1999; Paterson and Nordberg, 2000; Perry et al., 1995).

Absorption: galantamine has shown linear pharmacokinetics with a recommended dosage of 8–24 mg/day. It is freely absorbed, and has high bioavailability and a half-life in plasma of about 7 h, but plasma binding is low (only about 18%) (Bickel et al., 1991; Mihailova et al., 1989).

Distribution: repeated dosage of galantamine at about 12–16 mg twice a day gave a mean plasma concentration of about 42–137 ng/mL and the plasma concentration varied from 29 to 97 ng/mL. Galantamine does not accumulate, even after continuous usage of 6 months. When ingested with food, the

absorption of the drug is delayed but it does not affect overall absorption, and peak plasma concentration falls to about 25% (Jones et al., 1996).

Metabolism: Galantamine is mostly metabolized by cytochrome P-450 isozyme in the liver. Metabolites that are formed include O-desmethyl-galantamine, norgalantamine, O-desmethyl-norgalantamine, galantaminone, and epigalantamine. None of these are present in any notable AChE activities, and activity is largely on unmetabolized galantamine (Janssen, 2000).

Excretion: Renal excretion in a healthy person is about 20%−25% of total plasma clearance, elimination is decreased in patients with renal impairment, and a dose reduction has been recommended for such patients (Paterson and Nordberg, 2000; Janssen, July 11, 2000).

Galantamine in Alzheimer's disease

1. Considerable help from galantamine was shown on the ADAS-Cog ($P < .0001$) and CIBIC (74% of the galantamine and 59% of the placebo patients were found to be stable and improved afterward). The galantamine also presented a significant improvement in patients suffering from Alzheimer disease and cerebrovascular disease (Erkinjuntti et al., 2002).
2. A total of 345 subjects were studied, of which 229 patients completed the 3- and 6-month visits. Patients withdrew because of adverse events and insufficient response to the drug treatment. Forty-five percent of patients were male. The patients were taking a variety of drugs including antiepileptic, antipsychotic, and herbal medications. The regular starting dosage of galantamine was 9.7 ± 6.7 mg/day, and after continuing the treatment for 3 months the average dosage was increased to 14.6 ± 5.0 mg/day and after being on the treatment for 6 months the average dosage given was 15.2 ± 2.7 mg/day. After 3 months of assessment 65% of patients had an increased MMSE (mini mental state examination score) with a response rate up to 92%. Most of the patients also showed improvement in MMSE score after the assessment for 6 months, providing a response rate of up to 91%. Overall, after 3 months, 38% of subjects were marginally improved, 22% were well improved, and 4% improved greatly, whereas 28% were unchanged. After 6 months, 20% were unchanged, 26% were marginally improved, 32% were well improved, and 7% responded very well to galantamine. A follow-up study was conducted for 12 months on 194 patients, in which the long-term effects of galantamine were found to be positive on the progression of AD (Henry et al., 2006, 2007).
3. Several ad hoc analyses of patients treated with galantamine with an MMSE score ≤ 14 were reported, suggesting improved functional and cognitive behavior in mild to moderate levels of AD (Lanctot et al., 2003).
4. A statistically significant difference between the active treatment and placebo groups showed an improved NPI score (Tariot et al., 2000).

5. The authors conducted a mass study on patients suffering from AD with CVD, they used a four-point study for over 6 months. Twice as many patients were found to be responders as compared to placebo (33.6% vs. 17.2% on placebo, $P = 0.003$). The authors also recommended a starting dose of 4 mg/day as compared to the recommended dosage of 8 mg/day, and gradually increased it to 24 mg/day for a 6-month follow-up program. This outcome was also found to be consistent with some previous mass studies on AD patients (Erkinjuntti et al., 2003, 2008).
6. A 12-week, open-label study was conducted to check the tolerability of a 1-week titration schedule that ranged from 8 to 16 mg/day of galantamine. The study showed 1-week titration to extended-release galantamine 16 mg/day was found to be well tolerated. There were some gastrointestinal (GI)-related adverse reactions (Scharre et al., 2008).
7. Various research on cholinesterase inhibitors like galantamine, donepezil, and rivastigmine have shown that this class of drugs only offers primary symptomatic relief and temporary cognitive improvement, but does not slow down disease progression (Hardy and Selkoe, 2002; Li et al., 2004).
8. Galantamine has shown considerable protection against Ab and okadaic acid-induced toxicity in neuroblastoma cells, which in turn shows an improved stress response (Calciano et al., 2010).
9. Initiating early treatment with cholinesterase inhibitors in mild to moderate AD can help in maintaining higher functions, independence, and improved quality of life. In patients who were studied using a double-blind phased trial, the placebo group did not catch up with the treatment group (Raskind et al., 2000).
10. In an extended 12-month study conducted on 26 AD and 11 HC (Healthy Control) subjects using galantamine, the posterior cingulate and corpus callosum cross-sectional area of the brain were put in focus for DTI studies, with all images from previous studies and newer studies being aligned to minimize errors. The cross-sectional finding at the baseline showed the reduction in genu and splenium of corpus callosum and FA in the posterior body of the corpus callosum in the patients treated with galantamine as compared to the placebo group. This result was also found to be consistent with previous studies, but the effect of galantamine was not preserved after 6 months open-label treatment. FA changes over the time seemed more important as it was found to be declining in both neurodegenerative and healthy aging individuals (Head et al., 2004; Likitjaroen et al., 2012).
11. Galantamine and other second-generation cholinesterase inhibitors, such as donepezil and rivastigmine are FDA-approved drugs for AD. Despite having different pharmacological properties these drugs have been shown to improve efficacy. The medications belonging to cholinesterase inhibitors were also found to be most effective when taken four times per

week. The MMSE score was also seen to be improving (Herrmann and Lanctot, 2007; Mielke et al., 2012).

12. Many cholinesterase inhibitors, especially galantamine, produce undesirable side effects in patients, sometimes even resulting in discontinuation of therapy. To counter this, the authors have continued to enhance the development of intranasal sprays of galantamine and chitosan. They found that GH−chitosan complex did not negatively alter the pharmacological efficiency of the drug, instead they recorded a decreased AChE protein level as compared to oral and nasal galantamine. No signs of toxicity or histopathological manifestations were found, indicating the biocompatibility of galantamine and chitosan (Lilienfeld, 2002; Hanafy et al., 2016).
13. A study conducted in China indicated that galantamine improves cognition and also has antineuroinflammatory effects in mice. Galantamine inhibits gliosis, proinflammatory signaling molecules (NF-κB p65), cytokines, and increased proteins associated with synapse in the hippocampus. Galantamine also shows reduced inflammation in microglia (Yi et al., 2018)
14. Ten trails with a total of 6805 subjects was analyzed, in which treatment with galantamine showed a greater proportion of subjects with improved rating. All dosages were found to cause improvements except for 8 mg/day, and the range of 16−36 mg/day was most favorable. A greater effect was achieved in 6 months than 3 months, which showed an ADAS-cog score improvement. Prolonged-release formulations also had the same efficacy and adverse reactions as the twice-daily regimen (Loy and Schneider, 2006).
15. In seven industry-oriented multicenter phase II and III trails, one of 5 months, one of 13 weeks, one of 29 weeks, two of 6 months, and two of 12 weeks, galantamine showed significant effects at doses of 16−32 mg/day which were statistically significant. Only the dose of 6 mg/kg failed to show any significance. Two 3-months trial with ADAS-cog scale showed significant improvement, using 24−32 mg/day dosages (Olin and Schneider, 2002)
16. In a 6-month follow-up assessment study of 33 AD patients, galantamine was found to benefit about 66.7% patients in different areas (visual construction, concentration, orientation, short- and long-term memory, attention, language ability, judgment, fluency, CASI total, and CDR-SB) except for fluency, which was on a par with donepezil, whereas rivastigmine showed improvements in all aspects. This study also did not find the 8 mg/day dosage to be significant and did not reach an optimum plasma concentration (Lin et al., 2019).

Toxicology and adverse drug reactions

Galantamine is a relatively safe drug, and shows good tolerability with no particular adverse drug reactions to vital signs or changes in laboratory reports.

Adverse reactions occurred in less than 5% of patients when studied on a 5-month randomized trial. The maintenance dose was 16 mg/day, which was escalated to 24 mg/day after 4 weeks at least. The main side effects that caused patients to quit the therapy were nausea, vomiting, anorexia, and diarrhea (Tariot et al., 2000).

Galantamine's adverse effects are similar to those of other cholinesterase inhibitors; it causes gastrointestinal stress with increasing dosage, those on 8 and 16 mg/day are less likely to forfeit therapy as compared to increased dosages of galantamine (Olin and Schneider, 2002; Physicians Desk Reference, 2005).

Conclusion

As discussed above, galantamine is used in neurodegenerative diseases, it is easier to obtain from various plant sources, can be made in vitro, and also can be synthesized in labs. Galantamine has also been studied extensively for its pharmacology and mechanism of action, and has been described as having a dual mode of action. Galantamine has been used for treatment of Alzheimer's disease for a long time and various studies have been discussed ranging from short-term to long-term follow-up studies, and it has been observed that galantamine can be used for mild to moderate Alzheimer's disease and has produced very little to no side effects in patients. However, the drug is not very promising in advanced stages of the disease and cannot actually halt the progression of the disease. Future studies of this drug could open new ways to understand the pathway of Alzheimer's disease progression and aid in the production of alternative modified drugs.

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Naturally Occurring Chemicals Against Alzheimer's Disease

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Naturally Occurring Chemicals Against Alzheimer's Disease offers a detailed discussion on the roles, molecular mechanisms, toxicology, and clinical data on phytochemicals and plant-based extracts in relation to Alzheimer's disease (AD) in a single source. AD is a complex degenerative brain disease and the most common cause of dementia. More research is needed on drugs which are not only effective but also safer to use for a longer period. As such, research on phytochemicals and plant-based extracts has increased with advances in understanding molecular mechanisms and development of new formulations with better bioavailability and efficacy. This new resource examines the available phytochemicals and plants that are potentially effective and determines the role and molecular targets of these phytochemicals in combating AD.

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