Archives of Pharmaceutical Sciences Ain Shams University 2024; Vol. 8(2): 275-289

OPEN ACCESS | Pharmacognosy | Review Article

An Updated Review on the Neuroprotective Constituents of Genus *Gardenia*

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ABSTRACT

Central Nervous System (CNS) disorders include many diseases with different symptoms and causes. According to the American Psychiatric Association (APA), these disorders are classified into several categories according to the disease's etiology and progression. These include neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), and neuropsychiatric disorders which include depressive disorders, anxiety disorders, schizophrenia (SZ), etc. Neuroprotection refers to strategies aimed at preserving and protecting the health and function of the neurons. Natural Products have been used extensively in managing CNS disorders, some of which even affect the underlying pathways causing them. Genus *Gardenia*, a part of the Coffee family; Rubiaceae is widely used in traditional medicine for various purposes, including its potential neuroprotective properties. This review provides a comprehensive analysis of the existing evidence on the therapeutic potential of *Gardenia* in addressing neurodegenerative and neuropsychiatric disorders. It also sheds light on the antioxidant, anti-inflammatory, and mood-stabilizing effects of *Gardenia*'s active constituents, such as crocins, iridoids, and flavonoids in managing these debilitating conditions.

Keywords: *CNS disorders; Gardenia; Alzheimer's disease; Crocins; Iridoids.*

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Citation | Zedan MA, Mostafa NM, Youssef FS, Eldahshan OA, 2024. An Updated Review on the Neuroprotective Constituents of Genus *Gardeni*. Arch Pharm Sci ASU 8(2): 275-289

DOI: 10.21608/aps.2024.300590.1179

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 01 July 2024. **Accepted** 18 August 2024.

Published by: Ain Shams University, Faculty of Pharmacy

1. Introduction

Central Nervous System (CNS) disorders are a group of miscellaneous diseases that affect the brain's or the spinal cord's function and sometimes their structures; causing altered personality traits and delays in developmental milestones **[3]**. The American Psychiatric Association (APA) **[4]** defines and categorizes many but not all CNS disorders according to their different etiologies. One of the most important categories include neurodegenerative (ND) diseases which are characterized by delayed-onset declines in cognitive functions as represented in Alzheimer's disease (AD) and Parkinson's disease (PD), which are the two most common neurodegenerative diseases **[3, 5]**. On the cellular level, both AD and PD are characterized by the deposition of Amyloid-*β* peptides and *α*-synuclein protein (Lewy bodies) respectively, and significant neuronal damage **[3, 6]**. The symptoms of AD include: delayed loss of motor function compared to other forms of dementia, language discrepancies, misperception, behavioral changes, agitation, misjudgment, miscommunication, impaired awareness and thinking, and emotional indifference, while PD symptoms include progressive loss of muscle coordination; leading to motor disabilities **[7]**.

Neuropsychiatric disorders are a broad category of CNS illnesses that affect the brain's function and the patient's behavior. They include depressive disorders (DD), which manifest as a deterioration of both behavioral and social functions. According to the World Health Organization (WHO), millions worldwide suffer from depression, and it is expected to become the second most common cause of death **[3]**. Anxiety disorders are also among the major neuropsychiatric disorders, which are recently increasing in numbers due to the demands of the modern, stressful lifestyle **[8]**, where about 4 to 6% of the world population suffer from different types of anxiety disorders such as phobias, panic attacks, post-traumatic stress disorder (PTSD), etc. **[9]**. Schizophrenia (SZ) is one of the most profound neuropsychiatric disorders which can be defined by the presence of one of the following symptoms; hallucinations, delusions, anhedonia, abnormal speech, or abnormal behavior **[10]**. CNS disorders also include sleep/wake disorders. Sleep is a crucial activity for a healthy mental and physical state. Some chronic diseases such as hypertension, diabetes mellitus, and major depressive disorders are associated with insomnia or poor sleep quality which affects daily functions **[11]**. Epilepsy, which is one of the most significant CNS disorders, is mentioned by APA only as a comorbidity to other disorders, and not as a separate, defined category. As many as 50% of epileptic cases develop psychiatric disorders along their course. Epilepsy is a debilitating neurological disease that afflicts more than 70 million people worldwide **[12]**.

Neurodegenerative and neuropsychiatric disorders pose significant challenges to public health, with a rising prevalence worldwide and they present a substantial burden on individuals and healthcare systems around the world. The management of these diseases has always proposed a challenge due to the presence of the blood-brain barrier; which limits the use of several drugs **[3]**. The current medications used in managing CNS disorders; in addition to their severe side effects, only offer symptomatic relief. Therefore, the demand for natural, disease-modifying drugs for these disorders is rising. Natural products often show multi-targeted, pharmacological actions, so they propose a better option for managing the complex mechanisms of CNS disorders [**13]**.

Genus *Gardenia* belonging to the family Rubiaceae, has more than 140 species distributed from Africa to Oceania **[14]** The most common species of *Gardenia* is *Gardenia jasminoides* J.Ellis (GJE). GJE, also known as Cape jasmine or common gardenia (**Fig. 1.)**, is a popular species widely cultivated in China and the most extensively studied in this genus **[15]**. Other species include: *Gardenia taitensis* or Tahitian gardenia which is a tropical species native to Polynesia **[16]**, *Gardenia thunbergia*, also called wild or forest gardenia **(Fig. 1.)** and is native to Africa **[17]**, and *Gardenia gummifera*, which is a species only found in India **[18]**. The species among this genus share some common taxonomical features with some morphological distinction between the different species **[19]**. Generally, they are woody shrubs to trees with extra-axillary branching, their odorous, creamy white flowers are solitary and terminal; however, their color darkens into yellow to orange before they deteriorate **[19]**. *Gardenia* fruits are subglobular or obovoid and are characterized by thick pericarp and bony endocarp **[19]**. The fruits of some Gardenia species are edible such as *Gardenia jasminoides* Ellis and *Gardenia erubescens* **[20, 21]**.

Several important classes of natural products have been isolated from this genus such as iridoids, triterpenes, crocins, flavonoids, organic acids, and volatile compounds. The most widely studied compounds are the iridoids and crocins **[22]**. Iridoids are monoterpenoidal compounds isolated from several flowering families, including Rubiaceae **[23]**. Crocins are hydrophilic apocarotenoid esters extracted mainly from the fruit of *Gardenia jasminoides*, which is the most common species of *Gardenia.* Both classes have shown marked neuroprotective effects in different CNS disorders **[22]**.

A B

Fig.1. Photographs of; A) *Gardenia jasminoides* leaves and flowers, B) *Gardenia thunbergia* leaves and fruits **[1, 2]**.

Gardenia species have been traditionally used in herbal remedies for their calming and mood-stabilizing effects **[24]**. *Gardenia* species have various pharmacological uses including: 1) Antioxidant properties: *Gardenia* species help reduce oxidative stress and protect cells from damage. 2) Anti-inflammatory properties: *Gardenia* species contain compounds such as geniposide; which possesses anti-inflammatory activity through different mechanisms of action **[3]**. 3) Anti-anxiety and anti-depressant properties. **[24]**.

This review provides a comprehensive overview of the current understanding of *Gardenia*'s neuroprotective properties, highlighting the potential therapeutic implications of this traditional medicine in neuroprotection, focusing on the role of the secondary metabolites isolated from this genus.

2. Materials and Methods

The related information on the genus *Gardenia* and its isolated compounds was obtained from internationally recognized scientific databases and reputed publishers through the Internet (Web of Science, PubMed, Reaxys, American Chemical Society (ACS), MDPI, Springer Nature, Royal Society of Chemistry, Frontiers, Wiley Online Library, Elsevier, and Egyptian Knowledge Bank (EKB)). The search term used is: "*Gardenia*" separated with the Boolean operator (AND) from the following terms: "crocins", "iridoids", "phenolic compounds", "triterpenes", "neuroprotection", "central nervous system disease", and "CNS. The names of the species of *Gardenia* were retrieved from the International Plant Names Index (IPNI) **[23]**, and all the available literature about them was reviewed up to May 2024 to obtain information about the neuroprotective activity of *Gardenia* species. The inclusion criterion included articles where *Gardenia* was mentioned. Full-text articles were screened using the search terms previously mentioned in their titles, abstracts, or full text. The exclusion criteria were the gray literature, and the articles addressing the pharmacological actions of *Gardenia* species other than the neuroprotective, antioxidant, and anti-inflammatory purposes.

3. Results

Several classes of secondary metabolites were reported from the different species of *Gardenia*. The following classes possess a marked effect in the management of CNS diseases and disorders*:* crocins and neocons, iridoids and iridoid glycosides, flavonoids, organic acids, volatile compounds, monoterpenoids, and triterpenoids **[15]**.

3.1. Classes of neuroprotective secondary metabolites isolated from the genus *Gardenia*

3.1.1. Crocins

Crocins are water-soluble compounds belonging to apocarotenoids. Crocins are derived from lycopene through intricate and precise biosynthetic pathways; therefore they are difficult to synthesize artificially **[25]**. They are glycosides of crocetin (1); a twenty-carbon, polyene dicarboxylic acid. There are different types of crocins isolated mainly from *Gardenia* fruits and the stigmas of saffron (*Crocus sativus*). They exist in nature in *trans* form but a few *cis*-crocins were also isolated from *Gardenia* and *Crocus* **[26, 27]**. Crocin-I (2) is the most abundant type of crocins, followed by crocin-II (3), crocin- III (4) and crocin-IV (5) **[28, 29]**.

Neocrocins are also derivatives of crocetin but have an altered binding system of sugars compared to crocins. Neocrocin A (6), a novel crocin isolated by Uekusa *et al*; possesses a very similar structure to crocin-I (2). Ni *et al* later isolated a series of neocrocins from B to J (7-15), some of which exerted marked neuroprotective activities **[30-32]** (**Fig. 2.)**.

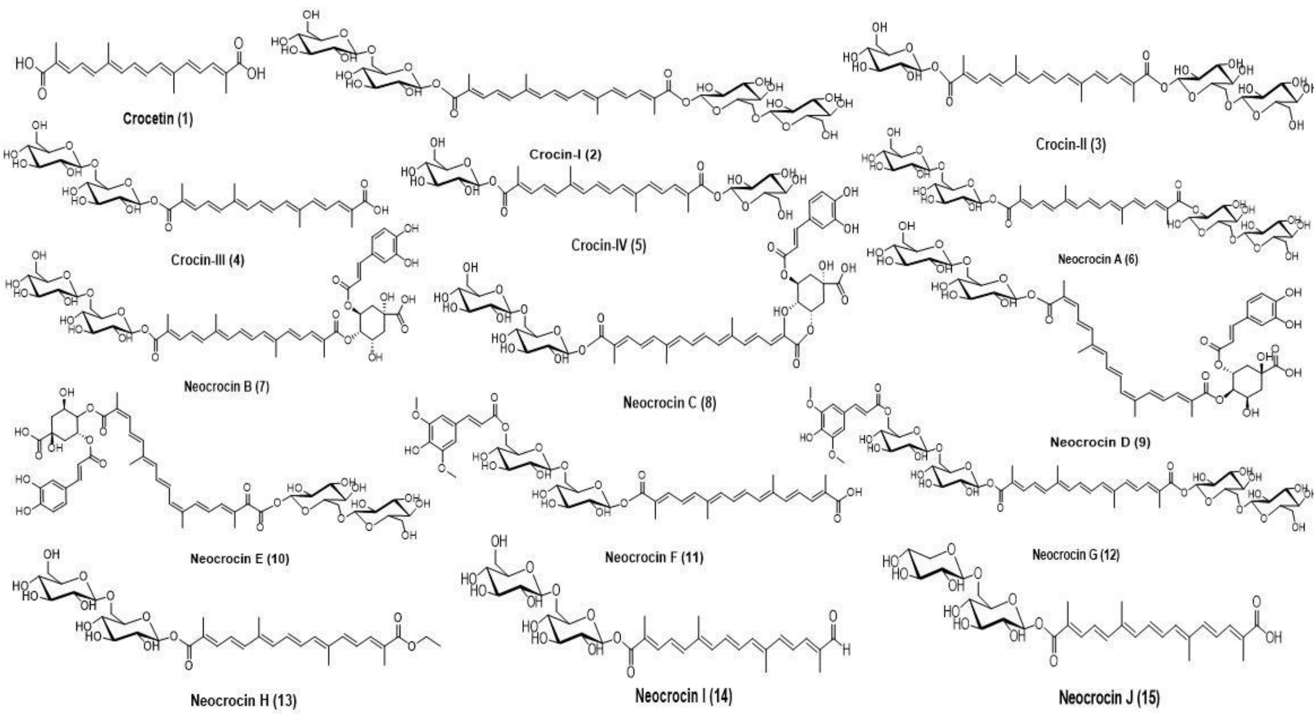

Fig.2. Some representative crocins and neocrocins isolated from *Gardenia* with reported neuroprotective effects.

3.1.2. Iridoids

Iridoids are a class of monoterpenoids containing a cyclopentane ring fused with a pyran ring. They are biosynthesized from the mevalonate pathway and they are intermediates in the biosynthesis of alkaloids **[33, 34]**. They mainly exist as glycosides but there are some iridoid aglycones such as genipin (16) which is isolated from *Gardenia* species and is a metabolite of geniposide (17) **[35]**. Geniposidic acid (18), genipin gentiobioside (19), garden side (20), gardoside (21), scandoside methyl ester (22), and shanzhiside (23) are all iridoid glycosides isolated from different organs of *Gardenia* species which possess neuroprotective effects in Alzheimer's disease, major depressive disorders, and Parkinson's disease **[36-40]** (**Fig. 3.)**.

3.1.3. Volatile compounds

Volatile monoterpenes are present in the flowers, seeds, leaves, fruits, and the gum resin of many species of *Gardenia* **[41-44]**. *Gardenia lucida* Roxb, an Indian species of *Gardenia*, yielded a volatile oil from its gum resin exudate; where α-pinene (24) and spathulenol (25) were the major components of this oil which showed anticonvulsant effect in status epilepticus **[45]**. The volatile contents of the seeds of *Gardenia* *jasminoides* also yielded linoleic acid (26); an essential, polyunsaturated fatty acid (PUFA) **[41, 46, 47]**. Linalool (27) was found to be the major compound in the essential oil of the flowers of *G. jasminoides* and *G. taitensis* **[43, 48, 49]** (**Fig. 4.)**.

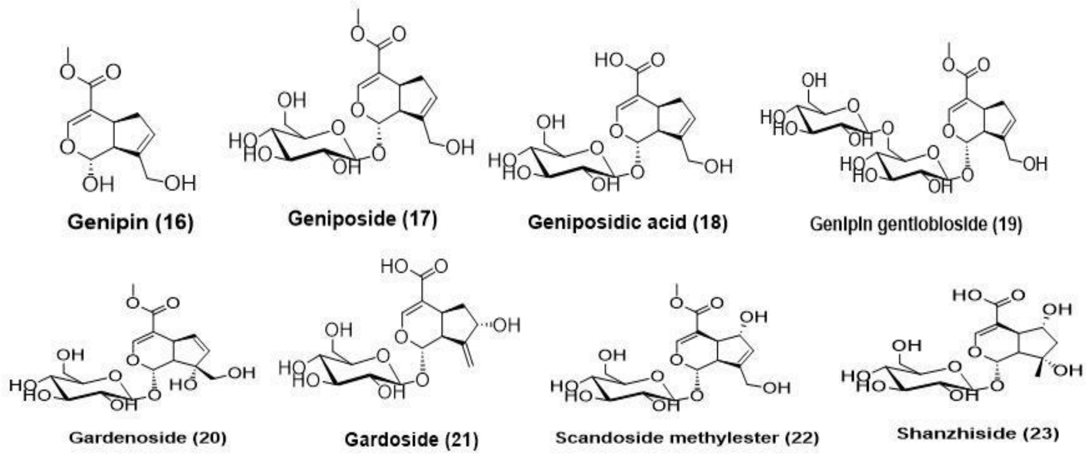

Fig. 3. Some representative iridoids and iridoid glycosides isolated from *Gardenia* with reported neuroprotective effects.

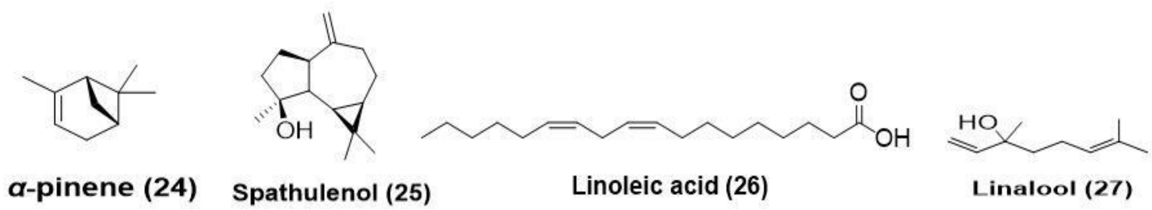

Fig. 4. Some representative volatile compounds isolated from *Gardenia* with reported neuroprotective effects.

3.1.4. Organic Acids

Quinic acid and its caffeic acid derivatives are polyphenolic acids isolated from *G. jasminoides*, *G.gummifera*, and *G.latifolia* **[42, 50-52]**. 3-*O*-caffeoylquinic acid, which is commonly known as chlorogenic acid (28) is one of the most abundant phenolic acids and possesses neuroprotective activities **[53, 54]**. Different organs of *G.jasminoides* yielded several chlorogenic acids such as cryptochlorogenic acid (29) and isochlorogenic acids A, B, and C (30, 31, 32) **[55]**. Quinic acid (33) itself was detected in the methanol extract of *G. gummifera* fruits **[42]**. Protocatechuic acid (34) is also a neuroprotective organic acid isolated from *G.jasminoides* fruits **[51]**. Quinic acid derivatives, especially chlorogenic acid (28), are involved in the reduction of oxidative stress and play a significant role in managing many neurological disorders **[53]** (**Fig. 5.).**

3.1.5. Flavonoids

A polymethoxyflavones series named gardenins is present in many species of *Gardenia* **[15, 56-58]**. Gardenin A (35), B (36), D (37), and E (38) are isolated specifically from the gum resin of *G. lucida*, *G. gummifera*, and *G. resinifera* Roxb **[56-58]**. 5-*O*-Desmethylnobiletin (39), a polymethoxy flavonoid ether, is also isolated from the gum resin or Dikamali gum of *G.lucida* **[59]**. Other flavonoids such as rutin (40), isoquercitrin (41), quercitin (42), etc are isolated from different species and organs in this genus **[15, 60-62]** (**Fig. 6.)**.

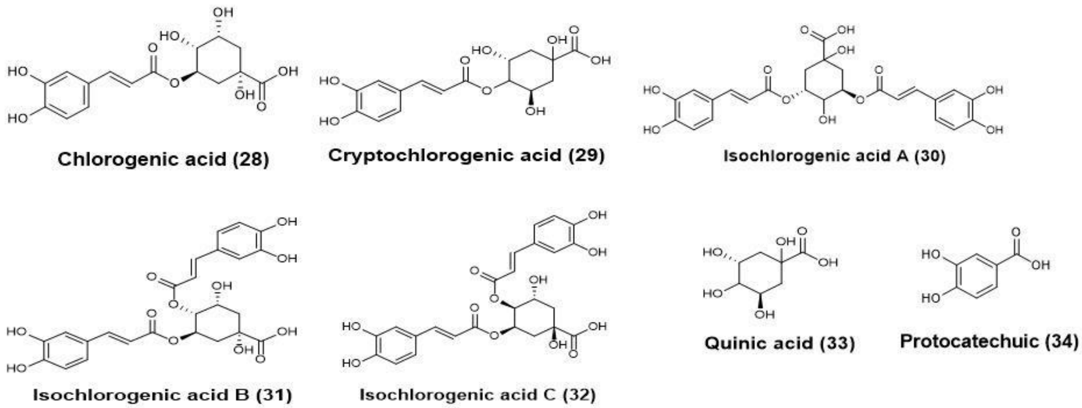

Fig. 5. Some representative organic acids isolated from *Gardenia* with reported neuroprotective effects.

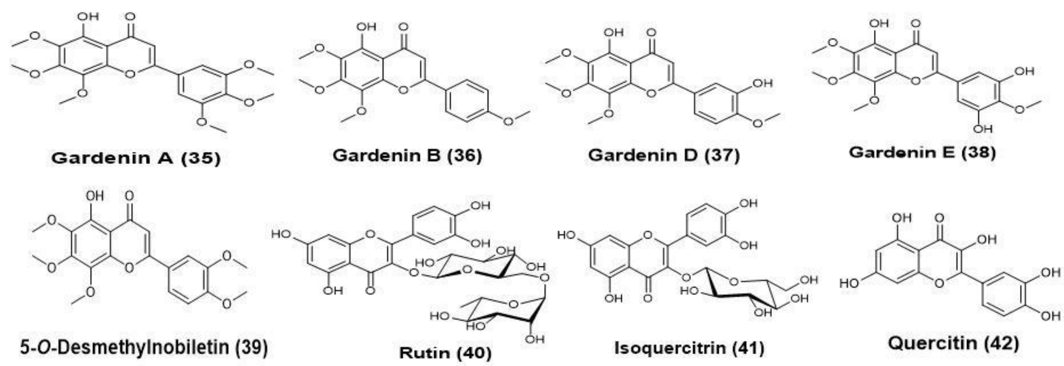

Fig. 6. Some representative flavonoids isolated from *Gardenia* with reported neuroprotective effects.

3.1.6. Triterpenes

Triterpenes were isolated from almost all known species in the genus *Gardenia* and they possess various pharmacological activities **[15, 60, 63-84]**. Cycloartane triterpenoids such as gardenolic acid A (43), B (44), and C (45) possess a potential neuroprotectant effect **[68]**. The Vietnamese species; *Gardenia philastrei* Pierre ex Pit. Yielded a new *seco*-cycloalkanes, named coronally acetate (46), and other compounds including; coronalolide (47), coronalolic acid (48), and coronoid methyl ester (49); which were previously isolated from *G.coronaria* and *G.thailandica* **[77, 84]**. Other *seco*-cycloalkanes include sootepin D (50) and G (51), which is also present in *G.philastrei*, while sootepin E (52), F (53), H (54), and I (55) were isolated from *G.sootepensis* in addition to sootepin G (51) **[64, 71, 72, 85, 86]**. A series of triterpene saponins; Erythrosaponins A–J are isolated from *G. erythroclada* Kurz; a species found in northern Thailand. Erythrosaponins D (56), F (57), G (58), I (59), and J (60) showed promising anti-inflammatory activity; which is important in managing the neuroinflammation associated with some neurodegenerative diseases **[70]**.

Although the presence of cycloalkanes and *seco*-cycloalkanes characterizes the genus *Gardenia*, other important neuromodulatory triterpenes such as ursolic acid (61) and its isomer oleanolic acid (62), were isolated from *G.jasminoides*, *G.saxatilis*, and *G.aqualla* **[51, 83, 87]** (**Fig. 7.)**.

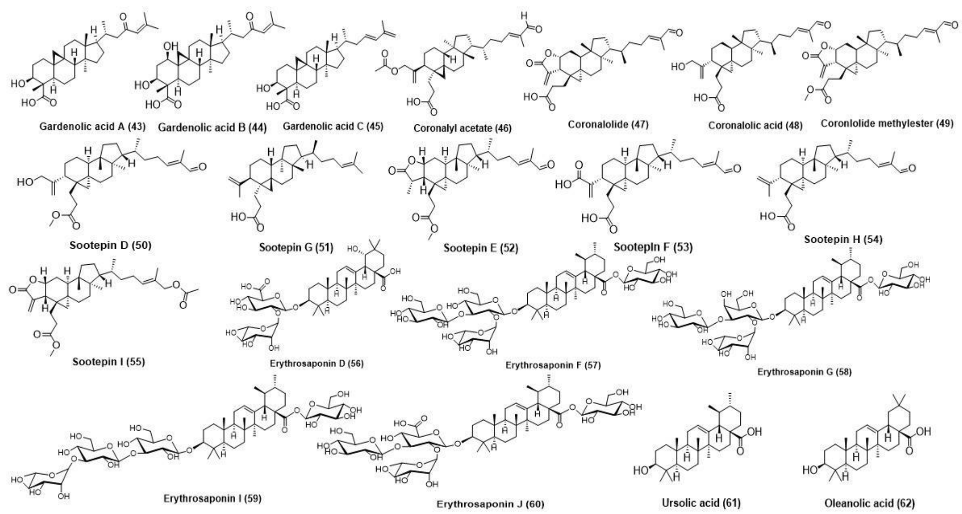

Fig. 7. Some representative triterpenes isolated from *Gardenia* with reported neuroprotective effects.

Conclusion

The *Gardenia* genus, a member of the Rubiaceae family, has long been recognized for its diverse array of bioactive compounds and their potential therapeutic applications. The genus's possession of various classes of phytochemicals, such as crocins, iridoids, triterpenes, volatile compounds, organic acids, and flavonoids, has garnered significant interest in exploring the neuroprotective properties of different *Gardenia* species. The synergistic interactions between these diverse phytochemicals may offer a multifaceted approach to addressing the complex mechanisms underlying neurodegenerative disorders **[15]**.

The current review provides updated information about the rich phytochemical profile of *Gardenia* species. Their neuroprotective effects suggest that these plants may be a promising source of natural compounds for developing therapeutic interventions targeting neurological conditions.

Additionally, throughout this review, we could conclude that *Gardenia jasminoides*, a Chinese species of *Gardenia*, is the most widely studied species in this genus. However, other less-studied species such as the African and the Indian species of *Gardenia*, are also sources of neuroprotective active compounds. This review also aims to assist future scientists in establishing a comprehensive database of potential neuroprotective elements for further *in-silico*, *in-vitro*, *in-vivo*, and clinical studies and experiments.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Publish

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing Interests

The authors declare that no competing interests exist.

Funding statement

The authors declare that no grants, funds, or any other support were gained during manuscript preparation.

Authors' Contributions

Conceptualization was performed by Omayma Eldahshan, data preparation and collection of the draft was performed by Mohga Zedan, and revision of the first draft was performed by Nada Mostafa, Fadia Youssef, and Omayma Eldahshan. All authors have read and approved the final manuscript.

Acknowledgments

The authors would like to acknowledge all colleagues in the Department of Pharmacognosy, Ain Shams University for their constant support. All authors read and approved the final manuscript.

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