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# Phytochemistry, Pharmacological Properties, and Ethnopharmacological Uses of *Glaucium* Mill. (Papaveraceae)

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**Review Article**

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## Abstract

The genus *Glaucium* Mill. (Papaveraceae), commonly referred to as horned poppies, comprises annual and perennial herbaceous plants native to the Mediterranean basin and widely distributed across southern Europe, North Africa, and Western to Central Asia. Several species of the genus have long been incorporated into traditional medical systems for the management of respiratory complaints, pain, inflammatory conditions, skin disorders, and gastrointestinal ailments. This extensive ethnopharmacological background has stimulated increasing scientific interest in the phytochemical composition and pharmacological potential of *Glaucium* species. Phytochemical investigations have demonstrated that *Glaucium* taxa possess a rich and structurally diverse secondary metabolite profile dominated by isoquinoline alkaloids. Aporphine-, protopine-, protoberberine-, and benzophenanthridine-type alkaloids, including glaucine, protopine, allocryptopine, sanguinarine, and chelerythrine, have been extensively identified and are regarded as the principal bioactive constituents of the genus. In addition to alkaloids, *Glaucium* species contain biologically relevant phenolic compounds, particularly flavonoids and phenolic acids, which contribute substantially to antioxidant-related effects. Pharmacological studies, conducted predominantly in vitro and in animal models, indicate that extracts, fractions, and isolated compounds derived from *Glaucium* species exhibit a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antimicrobial, neuroprotective, anticholinesterase, and anticancer-related effects. These activities are largely associated with alkaloid- and polyphenol-rich extracts and often involve multitarget mechanisms. This review critically summarizes current knowledge on the phytochemistry, pharmacological properties, and ethnopharmacological uses of *Glaucium* species. By integrating traditional knowledge with experimental evidence, the review highlights both the pharmacological relevance of the genus and the existing gaps in research, emphasizing the need for further systematic phytochemical, toxicological, and mechanistic studies to better elucidate the therapeutic potential and safety profiles of *Glaucium* taxa.

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## 1. Introduction

The Papaveraceae family is native primarily to temperate and subtropical regions of the Northern Hemisphere and has many horticultural and pharmaceutical important taxa (Kusman Saygi et al., 2023). Comprising approximately 48 genera and 920 species, Papaveraceae is characterized by high generic endemism, suggesting multiple diversification events within geographically restricted areas. The family exhibits remarkable ecological plasticity, spanning diverse habitats from coastal regions to high-altitude summits, and from arid deserts to forest understories and rocky outcrops (Peng et al., 2023).

Distinguished by high species richness, *Glaucium* Mill. (~28 species) is widely distributed across a broad geography extending from Southern Europe to Southwest Asia (Aykurt et al., 2017). Iran and Türkiye represent major diversity hotspots for the genus (Aslan, 2012). From a biomedical perspective, *Glaucium* species have attracted sustained interest because their traditional use has prompted systematic phytochemical and pharmacological investigations. Studies consistently indicate that isoquinoline alkaloids constitute the dominant and most extensively characterized metabolite class in the genus, while phenolic compounds represent an additional biologically relevant group. In contrast, terpenoid- and lipid-related constituents have been reported only sporadically and generally at minor or trace levels (Hamamcıoğlu et al., 2018; Akaberi et al., 2021). Alongside chemical profiling, a growing body of experimental evidence has reported diverse biological activities for *Glaucium* extracts and isolated constituents, including antioxidant, anti-inflammatory, antimicrobial, neuroprotective/ anticholinesterase, and anticancer-related effects (Akaberi et al., 2021; Kocanci et al., 2022).

In this review, we summarize the current evidence on the distribution, ethnopharmacological relevance, phytochemical composition, and pharmacological activities of *Glaucium* species, with particular emphasis on isoquinoline alkaloids and phenolic constituents as key drivers of the reported bioactivities.

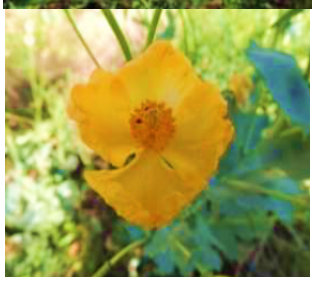
## 2. Papaveraceae Family and the Genus *Glaucium*

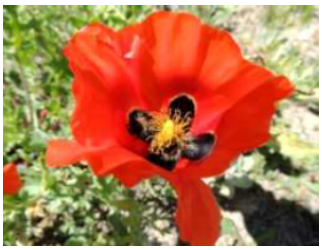
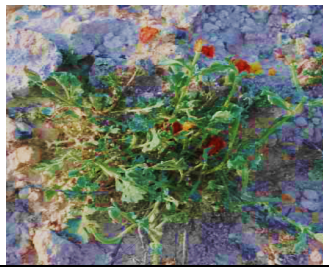
The Papaveraceae family, commonly known as the poppy family, is predominantly distributed across the temperate and subtropical regions of the Northern Hemisphere and comprises numerous species of horticultural and pharmaceutical importance (Kusman Saygi et al., 2023). This family includes approximately 48 genera and 920 species, with more than 70% of the genera being endemic to relatively restricted geographical regions (Peng et al., 2023). Members of Papaveraceae exhibit remarkable ecological adaptability, inhabiting a wide range of environments from sea level to elevations exceeding 6000 m, including forest understories, deserts, rocky cliffs, and alpine screes (Peng et al., 2024).

Within this diverse family, the genus *Glaucium* Mill. represents one of the most species-rich and widely distributed taxa. The genus comprises approximately 28 species, primarily native to southern Europe, the Mediterranean region, and central to south-western Asia (Aykurt et al., 2017). Notably, Iran and Türkiye emerge as major centers of species diversity for *Glaucium*, hosting 17 species and 12 taxa, respectively (Aslan, 2012; Yıldız et al., 2015). Species of the genus are represented by annual or perennial flowering plants characterized by their distinctive aromatic odor and showy flowers, typically displaying yellow, red, or orange coloration. Some *Glaucium* species distributed in Türkiye are shown in Table 1.

According to global distribution data, *Glaucium* species are natively distributed across Europe, Africa, Asia, Tropical Asia, and Australia (WFO, 2025) (Figure 1). Beyond their native ranges, several species have been introduced into non-native regions through human-mediated activities. The brown-colored areas in Figure 1 illustrate these introduced distributions, highlighting regions where *Glaucium* species have spread as a result of anthropogenic dispersal.

**Table 1.** Some *Glaucium* species distributed in Türkiye with their photographs

| Plant species | Plant photographs | Reference |
|---|---|---|
| *Glaucium alakirensis* (endemic) |  | (Aykurt et al., 2017) |
| *Glaucium acutidentatum* (endemic) |  | (Mungan, 2016) |
| *Glaucium cappadocicum* (endemic) |  | (Mungan, 2016) |
| *Glaucium corniculatum* var. *corniculatum* |  | (Kusman Saygi et al., 2023). |
| *Glaucium flavum* |  | (Mungan, 2016) |
| *Glaucium grandiflorum* subsp. *refractum* var. *torquatum* (endemic) |  | (Kusman Saygi et al., 2023). |

| | | |
|---|---|---|
| *Glaucium grandiflorum* var. *haussknechtii* |  | (Mungan, 2016) |
| *Glaucium leiocarpum* |  | (Mungan, 2016) |
| *Glaucium secmenii* (endemic) |  | (Yıldırımlı, 2012). |

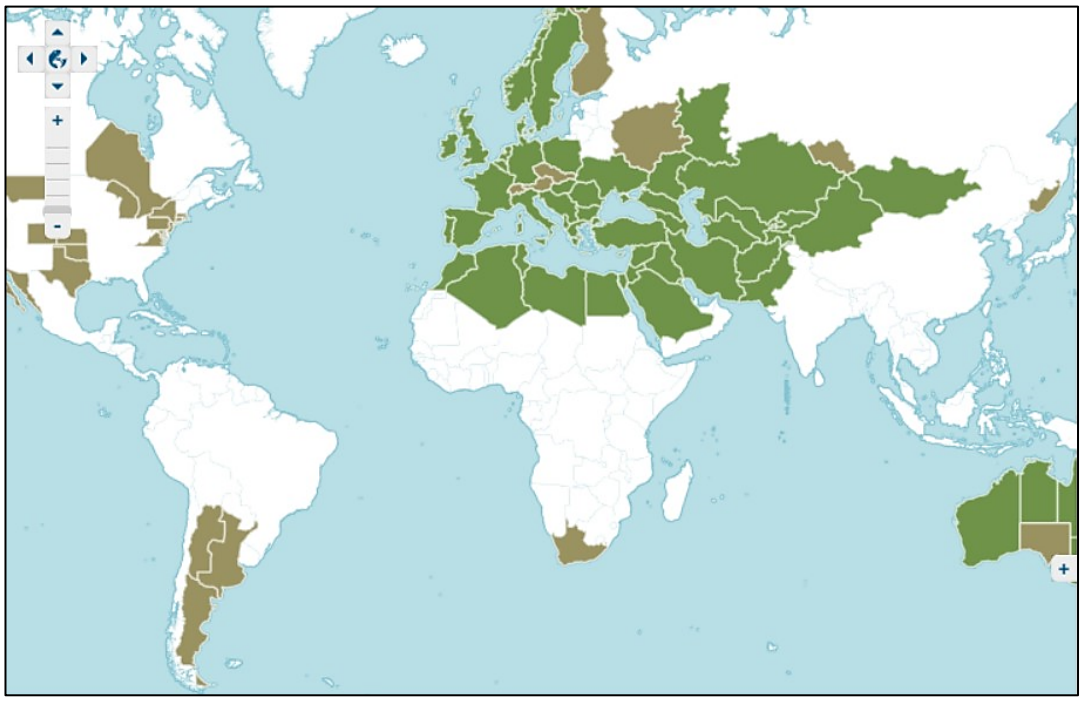


**Figure 1.** Global distribution pattern of the genus *Glaucium* (WFO, 2025). Native ranges are shown in green, while brown-colored areas indicate introduced distributions resulting from anthropogenic dispersal.

## 3. Phytochemical Composition of *Glaucium* Species

Since antiquity, plants have served as a fundamental source of medicinal agents. They synthesize a wide range of secondary metabolites, such as phenolic compounds, alkaloids, saponins, glycosides, resins, terpenes, and lactones, which play crucial roles in plant growth,

development, and reproduction, as well as in defense against pathogenic challenges (Elshafie et al., 2023). These plant-derived secondary metabolites, commonly referred to as phytochemicals, originate from primary metabolic pathways and exhibit diverse biological and pharmacological activities (Ozay et al., 2016).

Phytochemicals are widely distributed throughout the plant kingdom and are present not only in commonly consumed fruits and vegetables but also in numerous medicinal and wild plant species that have long been utilized in traditional healthcare systems. Increasing scientific interest in such non-cultivated and medicinal taxa has revealed that many of these plants represent particularly rich reservoirs of bioactive secondary metabolites with significant therapeutic potential (Alper & Özay, 2022). In this context, medicinal genera traditionally used in folk medicine, such as *Glaucium*, have attracted considerable attention as promising sources of pharmacologically active phytochemicals.

Many *Glaucium* species are traditionally employed as antitussive, analgesic, sedative, and narcotic agents, as well as in the treatment of skin, liver, and inflammatory disorders (Kusman Saygi et al., 2023). This long-standing ethnomedicinal use has stimulated extensive phytochemical investigations, leading to the identification of a rich and structurally diverse secondary metabolite profile within the genus. Although alkaloids have been the primary focus of most phytochemical studies on *Glaucium*, several investigations have also confirmed the presence of other phytochemical classes, including ketones, glycosides, fatty acids, alkenes, terpenes, and fatty alcohols, generally detected in minor or trace amounts (Hamamcioğlu et al., 2018). Among these constituents, alkaloids clearly represent the most abundant, chemically diverse, and biologically significant secondary metabolite class in the genus, forming the basis of many of its reported pharmacological effects.

### 3.1. Alkaloids

Alkaloids are secondary metabolites that exhibit a high degree of diversity not only in terms of their botanical and biochemical origins but also with respect to their chemical structures and pharmacological effects. Accordingly, several classification approaches have been proposed. Alkaloids may be classified based on their molecular precursors, core structural skeletons, biosynthetic origins, or the biochemical pathways involved in their formation (Dey et al., 2020).

In general, alkaloids are naturally occurring plant compounds containing at least one nitrogen atom, typically basic in character and structurally complex. A major milestone in alkaloid research was the isolation of the first alkaloid, morphine, from *Papaver somniferum* in 1804 (Dey et al., 2020). Based on their chemical structures, alkaloids are grouped into isoquinoline, indole, pyridine/piperidine, pyrrolidine, purine, imidazole, steroidal, and diterpenoid alkaloids (Yang et al., 2024). Within this framework, the genus *Glaucium* is distinguished by its richness in isoquinoline alkaloids, which represent the dominant and most extensively investigated secondary metabolite class in the genus (Akaberi et al., 2021). In a study on the aerial parts of *G. corniculatum*, six isoquinoline alkaloids—dehydroberberine, berberine, protopine, allocryptopine, corydine, and glaucine—were identified (Al-Saleem et al., 2024).

Alkaloids such as glaucine, protopine, isoboldine, allocryptopine, scoulerine, and corydine are of particular importance in *Glaucium* species, as they are both pharmacologically active and serve as chemotaxonomic markers for interspecific differentiation (Figure 2). These compounds have been extensively analyzed in species including *G. corniculatum, G. flavum, G. grandiflorum,* and *G. oxylobum*, with their presence and quantitative profiles confirmed using advanced analytical techniques such as HPLC and LC-MS/MS (Bournine et al., 2013a; Chang et al., 2015; Morteza-Semnani et al., 2005).

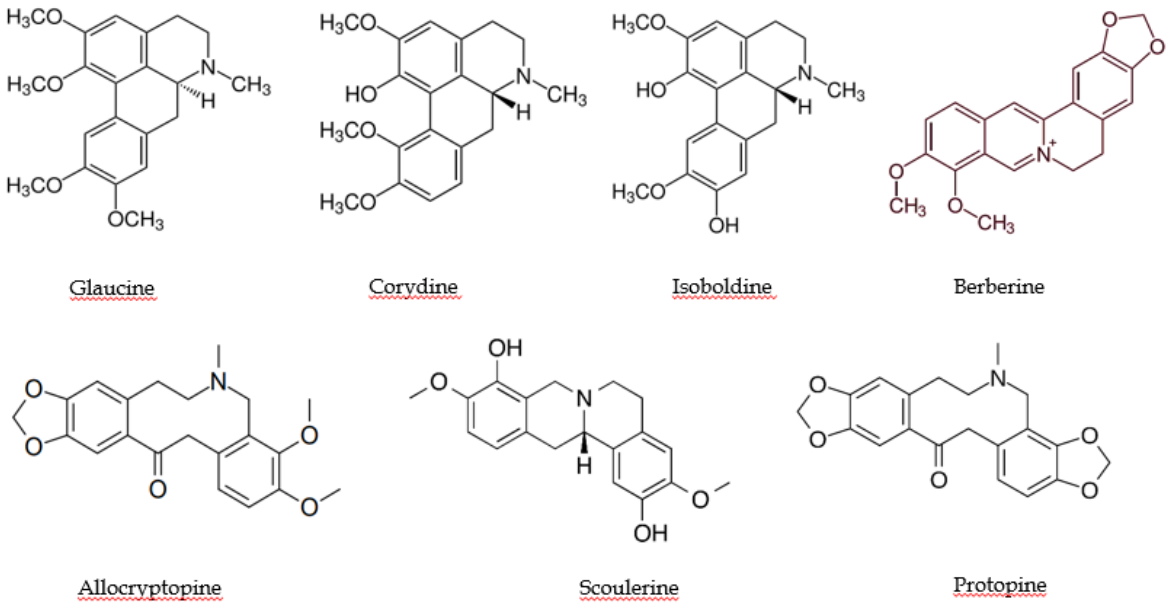



**Figure 2.** Major isoquinoline alkaloids most frequently reported in *Glaucium* species

Comprehensive reviews and recent analytical studies indicate that aporphine alkaloids predominate in the genus *Glaucium*, while other structural types—such as protopine, benzophenanthridine, benzylisoquinoline, protoberberine, and morphinan alkaloids—are also characteristic of the genus (Akaberi et al., 2021; Yagi et al., 2024). The aporphine alkaloid glaucine, first isolated from *G. flavum*, is widely distributed among *Glaucium* species and is used clinically as an antitussive agent; moreover, it has been reported to exhibit notable anticancer activity (Yagi et al., 2024).

GC–MS and chromatographic studies conducted on different *Glaucium* species and populations (e.g., *G. flavum, G. leiocarpum, G. corniculatum,* and *G. grandiflorum*) have revealed the presence of numerous alkaloids, including glaucine, isocorydine, protopine, allocryptopine, and dehydroberberine, as well as novel structures such as glauciumoline (Bozkurt et al., 2022; Demir et al., 2017; Kurkin et al., 2024; Kusman Saygi et al., 2023). The pronounced chemotypic and geographic variations observed in alkaloid profiles highlight the decisive roles of environmental conditions and genetic factors in shaping the phytochemical composition of the genus *Glaucium* (Bozkurt et al., 2024; Petitto et al., 2010).

### 3.2. Phenolic compounds

In addition to alkaloids, phenolic compounds constitute another major and biologically relevant class of secondary metabolites in *Glaucium* species, as demonstrated by several phytochemical investigations employing chromatographic and mass spectrometric techniques (Al-Saleem et al., 2024). Plant phenolics comprise a structurally diverse group of compounds characterized by one or more phenolic hydroxyl groups and are known to play essential roles in plant defense mechanisms, pigmentation, growth regulation, and responses to biotic and abiotic stress factors (Ozay et al., 2016). From a chemical perspective, phenolic compounds may occur as glycosides or aglycones, exist in free or matrix-bound forms, and appear as monomeric or polymeric structures, reflecting their substantial structural and functional diversity (Alara et al., 2021). Based on their core structures, phenolic compounds are commonly classified into phenolic acids, coumarins, flavonoids, stilbenes, lignans, and tannins (Ozay et al., 2024).

Phytochemical studies have shown that *Glaucium* species contain a broad spectrum of phenolic constituents, predominantly represented by flavonoids and phenolic acid derivatives (Figure

3), particularly hydroxycinnamic acid–related compounds (Kusman Saygi et al., 2023) These phenolics are mainly detected in the aerial parts of the plants, such as leaves, flowers, and stems, and are frequently present in glycosylated forms, a feature known to influence their solubility, stability, and biological activity (Hamamcioğlu et al., 2018). Owing to these properties, phenolic compounds substantially contribute to the antioxidant capacity of *Glaucium* extracts by enhancing free radical scavenging potential.

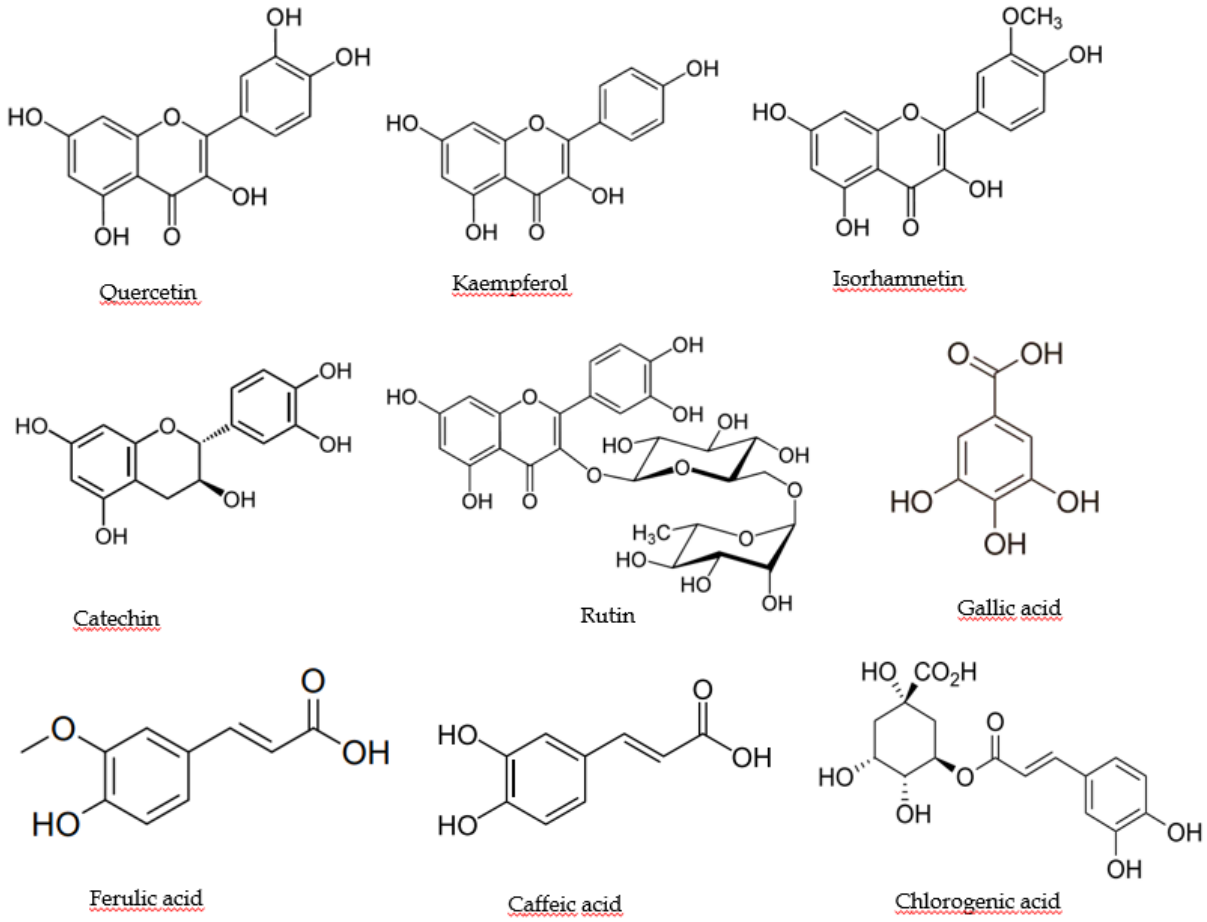



**Figure 3.** Major flavonoids and phenolic acids most frequently identified in *Glaucium* species

Species-specific investigations further illustrate the diversity of phenolic profiles within the genus. In *G. flavum*, seven phenolic compounds—kaempferol, caffeic acid, catechin hydrate, syringic acid, chlorogenic acid, isoquercitrin, and trans-hydroxycinnamic acid—have been identified (Boulaaba et al., 2019). Similarly, analyses of *G. alakirensis* (endemic) revealed the presence of gallic acid, catechin, chlorogenic acid, hydroxybenzoic acid, and quercetin, indicating a phenolic composition dominated by flavonoids and phenolic acids (Özcandır et al., 2024). In *G. acutidentatum*, coumaric acid and ferulic acid derivatives have been reported, alongside a flavonoid profile largely occurring in glycosylated form; only quercetin and isorhamnetin were detected as aglycones in methanolic extracts, whereas glycosides of quercetin, isorhamnetin, and kaempferol were more prevalent (Yagi et al., 2024). A detailed study on the aerial parts of *G. corniculatum* identified six flavonoids—quercetin, isorhamnetin, rutin, isorhamnetin-3-O-rutinoside, quercetin-3-O-glucoside-7-O-rutinoside, and isorhamnetin-3-O-glucoside-7-O-rutinoside—together with two hydroxycinnamic acid malate esters, namely phasilic acid and 2-O-feruloyl-L-malate, further highlighting the phenolic diversity of the genus (Al-Saleem et al., 2024).

Coumarins have also been reported within the phenolic fraction of *Glaucium*, although they appear to be minor and sporadically distributed constituents rather than dominant metabolites. Recent metabolomic investigations on *G. acutidentatum* detected coumarins alongside flavonoids and organic acids; however, these compounds were present within extract chemotypes clearly dominated by isoquinoline alkaloids such as glaucine (Yagi et al., 2024). In line with these findings, Akaberi et al. (2021) regard coumarins in *Glaucium* as underexplored minor components, for which no consistent structural series has been established across the genus and whose pharmacological profiles remain comparatively limited when contrasted with the extensively documented antioxidant, enzyme-inhibitory, and cytotoxic activities of alkaloids.

Overall, beyond alkaloids, *Glaucium* species exhibit a chemically rich phenolic profile dominated by flavonoids and phenolic acids, with contributions from coumarins and related compounds. This phenolic diversity, revealed primarily through modern LC–MS-based profiling approaches, underpins many of the antioxidant and complementary bioactivities reported for the genus and highlights phenolic compounds as important, albeit secondary, contributors to the pharmacological potential of *Glaucium* species.

## 4. Pharmacological Activities of *Glaucium* Species

Pharmacological studies conducted on *Glaucium* species have demonstrated that this genus exhibits a broad spectrum of biological activities, largely attributable to its phytochemical profile enriched in isoquinoline alkaloids (Akaberi et al., 2021). The available literature indicates that extracts, fractions, and isolated compounds obtained from various *Glaucium* species—particularly *G. flavum, G. grandiflorum, G. acutidentatum,* and *G. corniculatum*—possess notable pharmacological potential, especially with respect to anticholinesterase, antioxidant, and neuroprotective activities (Bournine et al., 2013b; Hamamcioğlu et al., 2018). In addition, a growing body of evidence has reported further biological effects of these species, including anticancer, antiproliferative, antimicrobial, and anti-inflammatory activities, underscoring the pharmacological relevance of the genus (Alsheikh et al., 2024; Altın, 2025)

### 4.1. Neuroprotective and anticholinesterase effects

Cell-based studies have consistently demonstrated that *Glaucium* extracts exert direct neuroprotective effects, particularly under conditions of oxidative stress. Methanolic and aqueous extracts of *G. corniculatum*, rich in flavonoids such as rutin and quercetin, were shown to prevent hydrogen peroxide ($H_2O_2$)-induced loss of viability in nerve growth factor (NGF)-differentiated PC12 cells while significantly preserving neurite number and length. In parallel, these extracts suppressed oxidative stress–induced acetylcholinesterase (AChE) upregulation at the mRNA level, whereas methanolic extracts additionally reduced AChE protein expression, highlighting a close association between flavonoid content and the observed neuroprotective activity (Kocanci et al., 2022). Beyond flavonoid-mediated effects, alkaloid-rich extracts have provided deeper mechanistic insights into *Glaucium*-derived neuroprotection. Allocryptopine-rich alkaloid extracts from *G. corniculatum* effectively suppressed oxidative stress–induced apoptosis in differentiated PC12 cells by reducing intracellular reactive oxygen species (ROS) levels, downregulating pro-apoptotic markers (Bax and caspase-3/9), upregulating the anti-apoptotic protein Bcl-2, and normalizing cell cycle distribution. These findings support a mitochondria-associated mechanism underlying the neuroprotective effects of *Glaucium* alkaloids (Dolanbay et al., 2021).

Comparable neuroprotective responses have been reported for *G. acutidentatum* and *G. corniculatum* using NGF-differentiated PC12 (dPC12) cells exposed to $H_2O_2$-induced oxidative stress. In these models, both alkaloid-rich methanolic and aqueous extracts exhibited pronounced anticholinesterase activity, producing 35–90% inhibition of AChE in vitro and significantly reducing cellular AChE activity. Concomitantly, the extracts attenuated oxidative

cytotoxicity in a dose-dependent manner. Notably, aqueous extracts of *G. corniculatum* exerted stronger neuroprotective effects than methanolic extracts, with maximal protection observed at concentrations of 500–1000 µg/mL, whereas extracts of *G. acutidentatum* displayed significant but comparatively moderate protection up to 500 µg/mL. All tested concentrations conferred statistically significant protection relative to the oxidative stress control, with maximal effects observed at higher extract doses (Kocanci et al., 2017a). Further support for the neuroprotective profile of *G. acutidentatum* was obtained from studies demonstrating that methanolic and aqueous extracts from its aerial parts significantly attenuated oxidative stress–induced cytotoxicity in dPC12 cells within the 100–500 µg/mL concentration range. In addition to preserving cell viability, these extracts promoted neurite outgrowth and modulated inflammatory responses by suppressing the pro-inflammatory cytokine IL-6 while enhancing levels of the anti-inflammatory cytokine IL-10. Collectively, these findings indicate that *G. acutidentatum* extracts exert neuroprotective effects through combined antioxidant and anti-inflammatory mechanisms (Hamamcıoğlu et al., 2018).

A consistent pharmacological hallmark of *Glaucium* species is potent cholinesterase inhibition, which complements their direct neuroprotective effects. In this context, purified isoquinoline alkaloids—including protopine, allocryptopine, and glaucine—isolated from the aerial parts of the endemic species *G. cappadocicum* were evaluated for anticholinesterase activity in vitro. Among these compounds, protopine exhibited the strongest AChE inhibitory activity (78.32% inhibition, $IC_{50}$ = 31.4 µg/mL), whereas allocryptopine and glaucine showed moderate inhibition, underscoring the contribution of specific alkaloid scaffolds to enzyme-targeted neuroprotection (Altın, 2025). Similarly, extracts obtained from the aerial parts of *G. alakirensis* demonstrated marked anticholinesterase activity, with the methanolic extract exhibiting the highest AChE inhibition (70.1%, $IC_{50}$ = 41.3 µg/mL) compared with ethyl acetate and n-hexane extracts. These results further suggest that polar extraction favors enrichment of bioactive cholinesterase-inhibiting constituents in *Glaucium* species (Delik et al., 2024).

At the level of isolated metabolites, isoquinoline alkaloids from *G. arabicum*, including glaucine, protopine, isocorydine, and norsanguinarine, were identified as potent cholinesterase inhibitors. Using the Ellman assay, glaucine showed the strongest AChE inhibition (84.1%, $IC_{50}$ = 9.6 µM), while protopine exhibited the highest BChE inhibitory activity (71.4%, $IC_{50}$ = 13.3 µM), supporting the dual cholinesterase inhibitory potential of *Glaucium*-derived alkaloids (Elbermawi et al., 2018). Consistent findings were reported for alkaloid fractions obtained from *G. corniculatum* var. *corniculatum* and *G. grandiflorum* subsp. *refractum* var. *torquatum*, which yielded several isoquinoline alkaloids, including sanguinarine and chelerythrine. Among these, sanguinarine exhibited the most potent AChE inhibition (87.6%, $IC_{50}$ = 8.4 µM), whereas glaucine showed notable BChE inhibitory activity. These results further highlight benzophenanthridine- and aporphine-type alkaloids as key contributors to the neuropharmacological profile of *Glaucium* species (Kusman Saygı et al., 2023).

Finally, multitarget neuroprotective activity has been demonstrated for *G. grandiflorum* var. *grandiflorum* and *G. corniculatum* subsp. *refractum*. A methanolic extract of *G. grandiflorum* exhibited strong AChE inhibition (~81% at 320 µg/mL), comparable to galantamine, and provided protection against oxidative DNA damage (Ozsoy et al., 2018). In parallel, an alkaloid-rich extract of *G. corniculatum*, characterized by high allocryptopine and protopine content, showed potent inhibitory activity against both AChE and BChE and additionally inhibited prolyl oligopeptidase, an enzyme implicated in neurodegenerative processes. These findings underscore the multitarget neuropharmacological potential of *Glaucium*-derived alkaloids (Bozkurt et al., 2024).

### 4.2. Antioxidant activity

Members of the genus *Glaucium* exhibit pronounced antioxidant potential, which is primarily attributed to their rich phenolic composition and, in certain taxa, may be further modulated by alkaloid-containing fractions. Accumulating evidence from in vitro studies indicates that extracts obtained from different *Glaucium* species effectively scavenge free radicals, enhance reducing capacity, and modulate redox homeostasis through multiple complementary mechanisms. In *G. flavum*, phenolic-enriched fractions containing compounds such as kaempferol, caffeic acid, catechin hydrate, syringic acid, and chlorogenic acid demonstrated strong antioxidant performance across several assays, including total antioxidant capacity, ferric reducing antioxidant power (FRAP), β-carotene bleaching inhibition, and free radical scavenging activity (Boulaaba et al., 2019). Beyond conventional extracts, green-synthesized gold nanoparticles (AuNPs) produced using *G. flavum* leaf extract were also reported to exhibit significant antioxidant activity alongside low cytotoxicity and acceptable biocompatibility, underscoring the contribution of *Glaucium*-derived phytochemicals to innovative antioxidant applications (Dehghani et al., 2023).

Consistent findings have been reported for *G. grandiflorum var. grandiflorum*, whose methanolic extract displayed robust antioxidant activity in multiple in vitro models. These effects were evidenced by inhibition of lipid peroxidation, strong 2,2-Diphenyl-1-picrylhydrazyl **(**DPPH**)** and 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) **(**ABTS) radical scavenging capacity, high FRAP reducing power, and pronounced hypochlorous acid scavenging, collectively reflecting broad redox-modulatory properties (Ozsoy et al., 2018).

The influence of extract polarity on antioxidant performance was further illustrated in *G. cappadocicum*. Extracts obtained from the aerial parts using solvents of different polarities were evaluated using DPPH radical scavenging and FRAP reducing power assays, alongside spectrophotometric determination of total phenolic and flavonoid contents. Methanolic and ethyl acetate extracts exhibited strong free radical scavenging and reducing capacities, which closely paralleled their high phenolic and flavonoid contents, whereas n-hexane extracts showed limited antioxidant activity. Overall, these results suggest that *G. cappadocicum* may represent a promising natural antioxidant source in oxidative stress–related biological processes (Altın, 2025).

A more comprehensive assessment was conducted for *G. acutidentatum*, in which the impact of different extraction techniques—maceration, homogenizer-assisted extraction, and infusion—on antioxidant activity was systematically examined. Antioxidant capacity was evaluated using a battery of in vitro assays, including DPPH and ABTS radical scavenging, FRAP and CUPRAC reducing power, and metal chelating activity. Methanolic extracts obtained via homogenizer-assisted extraction exhibited the highest total phenolic content and the strongest overall antioxidant performance, with elevated Trolox equivalent values and superior $Fe^{3+}$ and $Cu^{2+}$ reducing capacities. LC–MS/MS analyses revealed the presence of flavonoids, phenolic acids, and several isoquinoline alkaloids, particularly glaucine, and the authors emphasized that the observed antioxidant activity may arise from the combined contribution of phenolic constituents and alkaloids (Yagi et al., 2024).

Similarly, the endemic species *G. alakirensis* demonstrated notable antioxidant potential when evaluated using ethanolic extracts. HPLC analysis of the phenolic profile identified gallic acid, chlorogenic acid, catechin, quercetin, and hydroxybenzoic acid as major constituents. Functional antioxidant assays revealed a high, concentration-dependent DPPH radical scavenging capacity, which notably exceeded that of caffeic acid and rosmarinic acid used as positive controls. Furthermore, measurements of total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) indicated high TAS and low OSI values, reinforcing the view that *G. alakirensis* represents a strong natural antioxidant source with potential relevance in mitigating oxidative stress (Özcandır et al., 2024).

### 4.3. Anti-inflammatory activity

Anti-inflammatory properties of *Glaucium* species have been demonstrated across multiple experimental levels, including enzyme-based assays, cell culture models, and in vivo systems. At the enzyme level, the methanolic extract of *G. grandiflorum* var. *grandiflorum* inhibited cyclooxygenase-2 (COX-2) activity by approximately 69%, highlighting its relevance to inflammatory pathways and cancer chemoprevention (Ozsoy et al., 2018). Complementary mechanistic evidence was provided by studies on alkaloid extracts of *G. corniculatum* subsp. *refractum*, containing allocryptopine, tetrahydropalmatine, and tetrahydroberberine N-oxide. In BV-2 microglial cells, these alkaloid-rich extracts markedly suppressed lipopolysaccharide (LPS)-induced ROS production and downregulated the expression of iNOS, COX-2, and pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) through inhibition of the p38 MAPK signaling pathway, indicating a substantial attenuation of neuroinflammatory responses (Dolanbay et al., 2021). Collectively, these findings complement the strong in vitro antioxidant profiles reported for *Glaucium* species and suggest a dual antioxidant–anti-inflammatory mode of action that may be relevant to neurodegenerative and inflammatory disorders.

Further evidence for cell-based neuroprotective and anti-inflammatory activity has been obtained from studies on methanolic and aqueous extracts of *G. corniculatum* using a hydrogen peroxide ($H_2O_2$)-induced oxidative stress model in NGF-differentiated PC12 (dPC12) cells. Phytochemical analyses revealed rutin and quercetin as the major flavonoid constituents of both extracts, with higher concentrations detected in the methanolic extract. Functional assays demonstrated that the extracts were non-cytotoxic within the concentration range of 100–500 µg/mL and significantly attenuated oxidative stress–induced loss of cell viability. In parallel, both extracts suppressed the release of the pro-inflammatory cytokine interleukin-6 (IL-6) and dose-dependently increased levels of the anti-inflammatory cytokine interleukin-10 (IL-10), with the most pronounced effects observed for the aqueous extract at 500 µg/mL. Notably, this extract reduced IL-6 secretion by 79-fold relative to the $H_2O_2$-treated group and increased IL-10 secretion by 87-fold compared with untreated controls. These results indicate that rutin- and quercetin-rich extracts of *G. corniculatum* mitigate oxidative stress–associated neuronal damage through anti-inflammatory mechanisms and exhibit marked neuroprotective potential (Koçancı et al., 2017b).

Consistent with these in vitro observations, the anti-inflammatory activity of *G. grandiflorum* has also been confirmed in vivo using the carrageenan-induced hind paw edema model in Wistar albino rats. Intraperitoneal administration of the methanolic extract of aerial parts (leaves, stems, and flowers) at doses ranging from 20 to 200 mg/kg resulted in a significant, dose-dependent inhibition of paw edema. Notably, at 200 mg/kg, the extract exerted stronger inhibitory effects during the late phase of inflammation than the reference drug indomethacin (8–10 mg/kg), with statistically significant differences. These findings suggest that *G. grandiflorum* displays pronounced anti-inflammatory activity, particularly during the prostaglandin-mediated phase of inflammation, and underscore its potential as a source of bioactive anti-inflammatory compounds (Morteza-Semnani et al., 2002).

Finally, anti-inflammatory activity has also been demonstrated for *G. flavum* in macrophage-based models. Extracts obtained from the aerial parts of the plant, particularly the ethyl acetate (EA) fraction, were evaluated in LPS-stimulated RAW 264.7 murine macrophages. Treatment with the EA fraction at concentrations of 12.5–100 µg/mL significantly suppressed nitric oxide (NO) production in a concentration-dependent manner, with the strongest inhibition observed at 50 and 100 µg/mL. In contrast, petroleum ether and ethanol fractions exhibited comparatively weaker effects. These results indicate that phenolic-enriched fractions of *G. flavum*, especially the EA fraction, exert potent anti-inflammatory activity, likely through the inhibition of LPS-induced NO production in activated macrophages (Boulaaba et al., 2019).

### 4.4. Cytotoxic and anticancer activities

A growing body of evidence indicates that *Glaucium* species are a rich source of bioactive alkaloids, particularly isoquinoline derivatives, which exhibit antiproliferative and pro-apoptotic effects in various cancer cell models. Alkaloid-rich extracts of *G. acutidentatum* and *G. corniculatum* have been shown to exert dose-dependent antiproliferative activity against HT-29 colon and HeLa cervical cancer cell lines while concurrently retaining acetylcholinesterase inhibitory activity, suggesting their potential relevance for multitarget therapeutic strategies (Kocanci et al., 2017a). In addition, aqueous and methanolic extracts of *G. acutidentatum* demonstrated selective cytotoxicity toward human hypopharyngeal carcinoma cells, with minimal effects on other tested cell lines, further supporting a degree of tumor selectivity (Yagi et al., 2024).

Among the investigated species, *G. flavum* has emerged as one of the most extensively studied taxa with notable anticancer-related properties. Phenolic-rich fractions obtained from the shoots of *G. flavum* significantly inhibited the proliferation of MCF-7 breast cancer cells, with ethyl acetate fractions exhibiting the strongest activity alongside pronounced antioxidant and anti-inflammatory effects (Boulaaba et al., 2019). Furthermore, alkaloid extracts derived from the roots of *G. flavum* inhibited breast cancer cell growth in vitro and reduced both tumor growth and vascularization in a human glioma chorioallantoic membrane model, with protopine identified as a major constituent (Bournine et al., 2013b). Subsequent quantitative analyses revealed the presence of protopine and bocconoline, the latter displaying potent and relatively selective cytotoxicity against breast cancer cells ($IC_{50}$ = 7.8 μM) with low toxicity toward normal cells, implicating bocconoline as a key contributor to the observed anticancer effects (Bournine et al., 2013a). Consistently, studies conducted on A549 lung cancer cells reported reduced cell viability following *G. flavum* extract treatment, accompanied by upregulation of pro-apoptotic genes (p53, Bax, and Bad) and downregulation of the anti-apoptotic marker Bcl-2, indicating apoptosis induction via intrinsic pathways (Kalantari & Entezari, 2020).

The antiproliferative potential of endemic *G. cappadocicum* has also been explored. Extracts prepared from the aerial parts of this species exhibited measurable antiproliferative activity, prompting the isolation and characterization of the secondary metabolites responsible for these effects. As a result, several isoquinoline alkaloids—namely salutaridine, glaucine, norglaucine, isocorydine, norisocorydine, isoboldine, predicentrine, and corytuberine—were isolated from this species for the first time. The isolated alkaloids were evaluated against A549 lung and HT-29 colon cancer cell lines within a concentration range of 5–100 μM, with corytuberine exhibiting the most pronounced cytotoxic effect against A549 cells ($IC_{50}$ = 61.2 μM) (Altın, 2025).

In addition to classical antiproliferative studies, phytochemical investigation of the aerial parts of *G. arabicum* Fresen. led to the isolation of two previously undescribed isoquinoline alkaloids, araglaucine A and araglaucine B, along with several known alkaloids, including araglaucine C, *N*-methylcanadinium-, *N*-methylstylopine-, and protopine-type derivatives, as well as norsanguinarine. The biological activities of these compounds were evaluated using B16 melanoma cell lines. Among the tested molecules, (7R,14S)-trans-*N*-methylcanadinium nitrate showed notable inhibition of melanin synthesis (approximately 35%) at 5 μg/mL (12.01 μM), while exhibiting relatively low cytotoxicity (approximately 12%). Although the primary endpoint focused on anti-melanogenic activity rather than direct growth inhibition, these findings suggest that *Glaucium*-derived isoquinoline alkaloids may act as modulators of melanoma-associated cellular processes rather than classical cytotoxic anticancer agents (Elbermawi et al., 2018).

Finally, isoquinoline alkaloids isolated from the aerial parts of *G. corniculatum* var. *corniculatum* and *G. grandiflorum* subsp. *refractum* var. *torquatum* have been systematically evaluated for their cytotoxic potential in vitro. Following methanolic extraction and purification, major alkaloids—including chelerythrine, sanguinarine, glaucine, and protopine—were tested

against HeLa (cervical cancer) and MCF-7 (breast cancer) cell lines using the MTT assay. Chelerythrine isolated from *G. corniculatum* exhibited the most pronounced cytotoxic activity, with an $IC_{50}$ value of 11.2 μM against HeLa cells, whereas sanguinarine also demonstrated notable antiproliferative effects. In contrast, glaucine and protopine showed weaker but concentration-dependent cytotoxicity. Importantly, these results indicated that benzophenanthridine-type isoquinoline alkaloids possess stronger cytotoxic potential than aporphine-type derivatives, highlighting chelerythrine and sanguinarine as promising bioactive scaffolds for further investigation in anticancer drug discovery research (Kuşman Saygı et al., 2023).

### 4.5. Antimicrobial activity

Several studies have investigated the antibacterial and antifungal properties of different *Glaucium* species, revealing marked interspecific variability that appears to be strongly influenced by extraction methods, solvent polarity, and phytochemical composition.

The antibacterial and antifungal potential of the total methanolic extract and the alkaloid sub-fraction obtained from the flowering aerial parts of the Iranian endemic species *G. vitellinum* was evaluated in vitro by Mehrara et al. (2015). Antibacterial activity was assessed using the agar well diffusion method against *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, while minimum inhibitory concentration (MIC) values were determined by the microdilution assay. Both the crude methanolic extract and, more prominently, the alkaloid sub-fraction exhibited marked antibacterial activity against *S. aureus* and *S. typhi*, with the alkaloid fraction showing stronger efficacy (MIC values of 0.9 mg/mL and 11.7 mg/mL, respectively). In contrast, only limited activity was observed against Gram-negative bacteria, including *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. Antifungal evaluation using the disk diffusion method demonstrated no significant inhibition against tested dermatophytes (e.g., *Aspergillus flavus* and *Trichophyton mentagrophytes*); however, *Candida albicans* exhibited high sensitivity, particularly to the alkaloid sub-fraction, with an MIC value (0.02 mg/mL) comparable to that of nystatin. These findings suggest that the antifungal activity of *G. vitellinum* is largely attributable to its isoquinoline alkaloid content (Mehrara et al., 2015).

Similar antimicrobial investigations have been conducted on *G. alakirensis*, where antibacterial and antifungal activities of ethanol extracts were tested against *S. aureus*, *Enterococcus faecalis*, *E. coli*, *P. aeruginosa*, *Candida albicans*, and *Candida tropicalis*. The extracts were active against *E. coli*, *C. albicans*, and *C. tropicalis* at 50 μg/mL, while higher concentrations were required to inhibit *S. aureus* and *E. faecalis* (100 μg/mL) and *P. aeruginosa* (200 μg/mL), indicating a concentration-dependent antimicrobial response (Özcandır et al., 2024).

Broader comparative studies further support the influence of solvent polarity on antimicrobial efficacy. Methanolic and chloroform extracts from the aerial parts of *G. grandiflorum* Boiss. & A. Huet, *G. oxylobum* Boiss. & Buhse, and *G. paucilobum* demonstrated concentration-dependent antibacterial activity against *S. aureus*, *Streptococcus sanguinis*, *E. coli*, *P. aeruginosa*, and *K. pneumoniae*. While methanolic extracts exhibited selective activity, particularly against Gram-negative bacteria, chloroform extracts showed broader and stronger antibacterial effects across all tested strains, likely due to their enhanced capacity to solubilize non-polar bioactive constituents (Morteza-Semnani et al., 2005). In addition, the methanolic extract of *G. grandiflorum* var. *grandiflorum* was reported to be effective against *Candida krusei* (Tosun et al., 2006), and methanolic extracts of *G. elegans* displayed antibacterial activity against *S. aureus*, *E. coli*, *Salmonella enteritidis*, *Bacillus anthracis*, and *Proteus* species (Soureshjan & Heidari, 2014).

Conversely, not all studies report strong antimicrobial effects within the genus. In an evaluation of *G. vitellinum*, Hakemi Vala et al. (2017) observed no detectable inhibition zones for methanolic extracts or alkaloid fractions in disk diffusion assays. MIC analyses further indicated that methanolic extracts were ineffective against Gram-negative bacteria, whereas

the alkaloid fraction exhibited selective activity solely against *Salmonella typhimurium*. Collectively, these findings highlight the pronounced variability in antimicrobial efficacy among *Glaucium* species and underscore the critical role of phytochemical diversity and extract type in determining the antimicrobial spectrum.

### 4.6. Antidiabetic–related effects and enzyme inhibition

Recent studies have explored the potential of various *Glaucium* species to modulate diabetes-associated biochemical processes, particularly through the attenuation of oxidative stress and the inhibition of carbohydrate-digesting enzymes. The hydroalcoholic extract prepared from the aerial parts of *G. flavum* was evaluated in alloxan-induced diabetic male Wistar rats. Hyperglycemia was induced by a single dose of alloxan (120 mg/kg), followed by oral administration of the extract at 500 mg/kg (body weight basis). Treatment with the *G. flavum* extract significantly increased the activities of key antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), in both heart and brain tissues compared with the diabetic control group. Notably, the enhancement of antioxidant enzyme activities was more pronounced in brain tissue and, for certain parameters, exceeded the effects observed in the glibenclamide-treated group (5 μg/kg). These findings suggest that *G. flavum* extract primarily mitigates hyperglycemia-associated oxidative stress and strengthens endogenous antioxidant defenses, rather than acting as a direct hypoglycemic agent (Khoshvaghti et al., 2019).

Complementary evidence has been provided by a recent in vitro study examining the antidiabetic-related enzyme inhibitory potential of different extracts obtained from the aerial parts of *G. acutidentatum*. In this study, α-amylase and α-glucosidase inhibition assays revealed that methanolic extracts obtained by homogenizer-assisted extraction (HAE-M) and maceration (MAC-M) exhibited significantly stronger inhibitory activity than aqueous extracts. Among these, the HAE-M extract demonstrated the highest α-amylase inhibitory activity, while methanolic extracts overall showed superior enzyme suppression capacity. The enhanced inhibitory effects were attributed to the richer phytochemical composition of methanolic extracts, particularly their flavonoid and phenolic content, which are known to interfere with carbohydrate-digesting enzymes. Although these findings are limited to in vitro conditions, the observed α-amylase and α-glucosidase inhibition indicates that *G. acutidentatum* may contribute to the modulation of postprandial glucose metabolism, highlighting its potential as a natural source of enzyme inhibitors relevant to diabetes management (Yagi et al., 2024).

## 5. Ethnopharmacological Uses of *Glaucium* Species

Across the Mediterranean and West Asian regions, *Glaucium* (Papaveraceae) species have been widely used in folk medicine for respiratory complaints, particularly cough, as well as for sedative–hypnotic, narcotic, analgesic, gastrointestinal (laxative), and dermatological purposes. In certain regions, additional uses including diuretic, renal, antihemorrhoidal, and memory-related applications have also been reported (Mehdiyeva et al., 2025). Among the genus, *G. corniculatum* and *G. flavum* are the most frequently cited species in ethnobotanical surveys conducted across different geographical areas (Mehdiyeva et al., 2025; Zadali et al., 2022).

In Türkiye, ethnobotanical and pharmacognostic studies indicate that *Glaucium* species have traditionally been employed in the treatment of headaches, eye disorders, wound healing, joint pain, constipation, and liver-related ailments. These uses are consistent with their reported antitussive, sedative, narcotic, analgesic, and antihemorrhoidal properties, as well as their application in various skin disorders (Bozkurt et al., 2022; Yagi et al., 2024). The ethnobotanical uses of *Glaucium* species in Türkiye are summarized in Table 2. Experimental studies further

suggest that *Glaucium* taxa exhibit antimicrobial, anti-inflammatory, antitumoral, and analgesic activities, which are largely attributed to their rich secondary metabolite profiles, including isoquinoline alkaloids (Hamamcıoğlu et al., 2018).

Species-specific ethnobotanical records highlight distinct regional practices. *G. grandiflorum*, native to the Eastern Mediterranean and Iran, has been traditionally used in Türkiye for blood purification and the treatment of eye diseases (Özsoy et al., 2018). *G. corniculatum* subsp. *corniculatum* and *G. leiocarpum* are widely known in Türkiye for their sedative and antitussive effects; in some regions, their leaves are also consumed as food, particularly as pastry fillings (Saday, 2009; Deniz et al., 2010). Outside Türkiye, *G. flavum* has a long history of use in Sicily, especially in the Aegadian Islands, where internal administration was limited due to potential nervous system effects, while external application was preferred. In this context, the species has been traditionally used for skin disorders and, more distinctively, for the topical treatment of hematomas, representing a culturally specific therapeutic practice (La Rosa et al., 2021).

Given the high alkaloid content of *Glaucium* species, their ethnomedicinal applications are predominantly associated with central nervous system, respiratory, and pain-related indications. Nevertheless, these traditional uses should be interpreted strictly within the framework of folk medicine rather than clinical efficacy, considering the potential toxicity and variability related to dosage and preparation methods.

**Table 2.** Ethnomedicinal Uses of *Glaucium* Species in Türkiye

| Plant species | Turkish common name | Plant part used | Traditional use (indication) | Preparation / administration | Reference |
|---|---|---|---|---|---|
| *Glaucium leiocarpum* | Boynuzlu gelincik | Leaves, stem | Antitussive; sedative (sleep-promoting) | Decoction (herbal tea) | (Deniz et al., 2010) |
| *Glaucium leiocarpum* | Boynuzlu gelincik | Leaves | Headache | Smoked in cigarette form (external administration) | (Erbay et al., 2018) |
| *Glaucium leiocarpum* | Boynuzlu gelincik | Flowers | Wound healing | Crushed with olive oil | (Bulut et al., 2017) |
| *Glaucium leiocarpum* | Boynuzlu gelincik | Leaves | Food use | Cooked by frying with onion | (Eşen, 2008) |
| *Glaucium leiocarpum* | Boynuzlu gelincik | Flowers, leaves | Diarrhea; headache | Decoction; wrapped with tobacco and smoked (external administration) | (Tuzlacı & Doğan, 2010) |
| *Glaucium grandiflorum* | Sarı gelincik | Fruits | Blood cleansing; eye ailments | Boiled and taken orally | (Ozsoy et al., 2018) |
| *Glaucium flavum* | Sarı haşhaş | Aerial parts | Wart treatment | Crushed and applied directly to the skin | (Emre et al., 2021) |
| *Glaucium corniculatum* | Kızıl gelincik | Fruit, root, whole plant | Eye disorders; burns; conjunctivitis; headache | Poultice; boiled aqueous preparation | (Bozkurt et al., 2022) |
| *Glaucium corniculatum* | Kızıl gelincik | Leaves | Food use | Cooked by frying with onion | (Eşen, 2008) |
| *Glaucium corniculatum* | Kızıl gelincik | Flowers | Stress relief; sedative use | Infusion | (Erucar et al., 2023) |

| | | | | | |
|---|---|---|---|---|---|
| *Glaucium cappadocicum* | Kapadokya haşhaşı | Whole plant | Antioxidant; antimicrobial | Ethanol extract; topical use | (Altın & Köksal, 2024) |

## 6. Conclusion and Future Perspectives

The observed variability across biological assays highlights the intrinsic complexity of plant secondary metabolism. The pharmacological performance of plant extracts is strongly dependent on both the qualitative and quantitative composition of secondary metabolites, which are in turn shaped by multiple factors such as geographical origin, environmental conditions, soil characteristics, altitude, and plant developmental stage (Jain et al., 2019; Özay & Pehlivan, 2024). This inherent variability underscores the necessity of strategically designed extraction and fractionation approaches to selectively enrich bioactive constituents relevant to specific pharmacological targets.

Despite increasing research interest, the available evidence indicates that a substantial proportion of *Glaucium* species remain insufficiently explored from both phytochemical and pharmacological perspectives, with *G. flavum* clearly representing the most extensively investigated taxon to date. Systematic characterization of phytochemical profiles across the genus is therefore essential to clarify chemotaxonomic relationships, elucidate intra- and interspecific chemical variability, and identify novel bioactive compounds with therapeutic relevance.

In agreement with extract-based findings, studies focusing on isolated isoquinoline alkaloids from *Glaucium* species have demonstrated that compounds such as glaucine, protopine, and sanguinarine often exhibit stronger and more selective inhibitory effects against acetylcholinesterase and butyrylcholinesterase than corresponding crude extracts. These observations highlight the importance of alkaloid scaffolds as key contributors to the neuropharmacological potential of the genus. Furthermore, the experimentally observed high antioxidant activities in certain *Glaucium* species indicate that this genus may possess protective potential against oxidative stress–induced cellular damage.

Taken together, these findings position *Glaucium* species as promising sources of multifunctional phytochemicals that integrate neuroprotective, antioxidant, anti-inflammatory, antimicrobial, and anticancer-related activities. Although most current evidence is derived from in vitro systems and rodent models, the convergence of ethnopharmacological relevance, phytochemical richness, and experimentally validated bioactivities warrants deeper pharmacological, toxicological, and mechanistic investigations. Future studies integrating advanced metabolomic profiling, target-based assays, and well-designed in vivo models will be critical to translating the traditional and experimental knowledge of *Glaucium* species into scientifically grounded pharmacological applications.

## Authorship Contribution Statement

The author is solely responsible for the conceptualization, methodology, data collection, analysis, and manuscript preparation.

## Conflict of Interest

The author declares no conflict of interest.

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