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Therapeutic potential of *Glycyrrhiza glabra* L. in managing oxidative stress-induced disorders

Dhritika Pandey[1,†], Vishwesh Dubey[1,†], Anupriya Singh[2]

Abstract

Oxidative stress is a critical factor in the pathogenesis of various diseases, including cancers, neurodegenerative disorders, and inflammatory conditions. *Glycyrrhiza glabra* L., commonly known as licorice, has been utilized in traditional medicine systems for its therapeutic benefits, particularly its rejuvenating properties. This review provides a detailed examination of the ethnopharmacological applications, global distribution, and phytochemical composition of *G. glabra*. Furthermore, the key bioactive molecules of *G. glabra*, such as glycyrrhizin, glycyrrhizinic acid, and isoliquiritin, are highlighted for their roles in counteracting oxidative stress. These phytomolecules have been shown to exert significant effects through mechanisms such as modulation of antioxidant enzyme activities and inhibition of free radical production. Comprehensive literature searches were performed across major scientific databases, including PubMed, Web of Science, PMC, Google Scholar, Springer, ScienceDirect, and Research Gate, to synthesize information on *G. glabra*. The review explores how these phytomolecules contribute to the mitigation of oxidative stress-related disorders, including cancer, neurodegenerative diseases, and inflammatory conditions. By synthesizing data from experimental studies, this review underscores the therapeutic potential of *G. glabra* in managing oxidative stress-induced conditions. It also identifies gaps in the current understanding of its molecular mechanisms and suggests the need for further research, to enhance its application in therapeutic settings. Future studies shall focus on elucidating the synergistic effects of bioactive compounds of *G. glabra* and their integration into clinical practice and integrative research to fully exploit its medicinal benefits.

Keywords:

Glycyrrhiza glabra, glycyrrhizin, neurodegenerative disorder, oxidative stress, *Rasayan*, *Yashtimadhu*

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Introduction

Oxidative stress, marked by excessive reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS), leads to cellular damage and is linked to various diseases, including cancer and neurological disorders.[1-3] While antioxidants can neutralize these harmful radicals, their efficacy may be compromised under high oxidative stress, making external sources essential for maintaining cellular health.[2,4,5]

In traditional medicine, "*Rasayana* drugs" are renowned for their rejuvenating and antioxidant properties. *Glycyrrhiza glabra*, commonly known as licorice and referred to as *Yashtimadhu* in Sanskrit, is a prominent *Rasayana* herb in Ayurveda. It is classified as a *Medhya Rasayana*, which enhances cognitive function and overall well-being. Traditionally, it is consumed in powdered form with milk for its *Medhya Rasayana* benefits.[6] *G. glabra* belongs to family *Fabaceae* and has long been extensively valued for its ethnopharmacological properties in India, as well as China and

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Southern Europe.[7,8] There are over 30 species within the *Glycyrrhiza* genus widely distributed around the world.[9]

This review examines distribution, traditional uses, and phytochemical properties of *G. glabra*, focusing on its major active compounds like glycyrrhizin, glycyrrhizic acid, etc. It assesses the role of *G. glabra* in countering oxidative stress and the potential therapeutic applications in managing oxidative stress-related disorders. Integrating traditional knowledge with current research, this review aims to provide insights into therapeutic potential and highlight areas for future research.

Methodology

This review article is based on a thorough analysis of research on *G. glabra*. Comprehensive literature searches were performed using keywords such as "*G. glabra*," "*Yashtimadhu*," "licorice," "antioxidant," "liquorice," and related terms across major scientific databases, including PubMed, Web of Science, PMC, Google Scholar, Springer, ScienceDirect, and ResearchGate. The review focused on studies addressing the phytochemistry, pharmacokinetics of major active phytomolecules, pharmacological activity, antioxidant effects, and health benefits of *G. glabra*. Articles were selected during April to June 2024. Studies not related to biosynthesis methods and metabolic reactions were excluded, and only English-language publications were considered.

Botanical description

G. glabra thrives in subtropical and temperate regions with fertile soil (pH 5.5–8.2) and annual rainfall of 400–1160 mm. The plant features compound, pinnate leaves with smooth, oblong leaflets (15 cm long) in 4–7 pairs. Its flowers, growing on axillary spikes, are stalkless, slender (0.8–1.2 cm), and range from lavender to violet. The fruit, a smooth-skinned pod (2–3 cm), contains 3–8 kidney-shaped seeds (~2 mm, dark green).[10]

The plant is taprooted and horizontally woody, often branching into 3–5 roots, with a brown-green to dark brown color. Roots typically penetrate up to 1 m but may extend to 6–8 m for underground water in dry conditions. They mature in 3–4 years, yielding 2–3 tons of dried roots per crop. Roots are thick, fibrous, and branched, with a yellowish interior, a sweet flavor, and an aromatic fragrance. The bark is brownish-green to dark brown.[10-13]

Geographical distribution

G. glabra is known to be native of Mediterranean basin.[14] From Eurasia to Western Asia, it is found in range of locations as demonstrated in Figure 1. In India, it is found in regions like Jammu and Kashmir, Punjab, and the Sub-Himalayan areas.[15]

Ethnomedicinal uses

The ethnomedicinal uses of *G. glabra*, frequently described in the world's renowned medical systems such as Ayurveda, Unani, Chinese, Korean, Japanese, African, and European traditional medical systems, have a rich historical backdrop. Throughout history, ancient civilizations, including the Egyptians, Chinese, Greeks, Indians, and Romans, have utilized the dried rhizome and root of this plant for medicinal purposes, primarily as an expectorant and carminative [Table 1].[16]

Phytochemistry

More than 400 phytomolecules have been isolated from *Glycyrrhiza* species of saponin, flavonoids, coumarins, chalcones, volatile, and essential oils. Numerous biologically active compounds have been isolated from various licorice parts, most of which are water-soluble.[9,10] The root of *G. glabra* contains several significant active phytomolecules across various classes of secondary metabolites pertinent to the condition under review [see Table 2]. Additionally, other phytomolecules from different classes of secondary metabolites have been isolated and are described below.

Pharmacology of *G. glabra* and its major active phytoconstituents

Several pharmacological activities of licorice have been documented to date and examined through both *in vitro* and *in vivo* models.[48] The antioxidant potential of aqueous and methanol extracts of *G. glabra* was evaluated against ascorbic acid. Both the 1,1-diphenyl-2-picrylhydrazyl (DPPH) and ferric reducing antioxidant power (FRAP) assays demonstrated that these extracts exhibit antioxidant activity comparable to that of ascorbic acid.[39] This review aims to compile studies on the pharmacological properties of licorice and its major active phytomolecules, focusing on their effects on oxidative stress-induced disorders, including anticancer, neurodegenerative, and inflammatory conditions [Table 3].

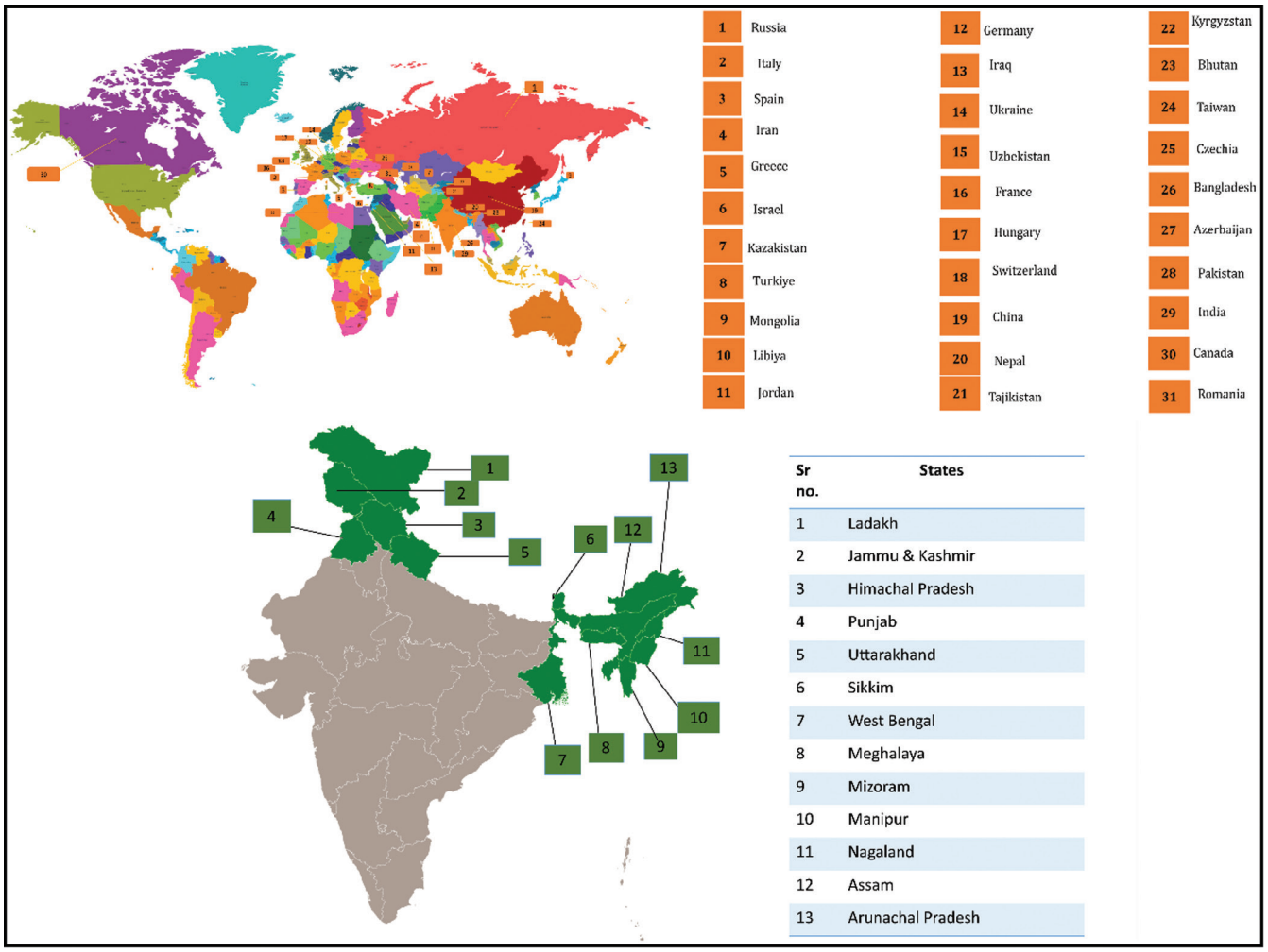
Antioxidant activity of major phytoconstituents of *G. glabra*

Glabridin

Research shows that glabridin's B-ring hydroxyl groups are key to its antioxidative effects. It reduces oxidative stress in macrophages by inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and increasing glutathione (GSH) levels. Additionally, it prevents lipid peroxidation in rat liver microsomes and protects mitochondrial function from oxidative damage.[68]

Licochalcones

Licochalcones A, B, C, D, and echinatin demonstrated effectiveness in preventing microsomal peroxidation triggered by Fe (III)-ADP/NADPH. Among them,



Sr no.	States
1	Ladakh
2	Jammu & Kashmir
3	Himachal Pradesh
4	Punjab
5	Uttarakhand
6	Sikkim
7	West Bengal
8	Meghalaya
9	Mizoram
10	Manipur
11	Nagaland
12	Assam
13	Arunachal Pradesh

Figure 1: Geographical distribution of *Glycyrrhiza glabra*. The green brackets represent the geographical distribution of the plant within India

licochalcones B and D exhibited strong antioxidative properties and acted as effective scavengers of superoxide.[69]

Glycyrrhizin

Glycyrrhizin reduces lipid peroxidation and GSH levels while increasing IFN-γ and decreasing IL-4 in blood and nasal mucosa, protecting against oxidative injury and enhancing immune response in allergic rhinitis. Its inhibitory effects are stronger at higher concentrations.[70]

Quercetin

Antioxidant properties of quercetin stem from its hydroxyl groups and catechol-type B-ring, with key features, including a catechol group, a 2,3-double bond, and hydroxylation at positions 3, 5, 7, 3′, and 4′.[71,73]

Isoliquiritigenin

Isoliquiritigenin, a flavonoid phytochemical, has shown potent cellular antioxidant properties. It suppresses the overproduction of ROS and preserves the enzymatic antioxidant defense system.[72]

Role of oxidative stress in cancer

Hydroxyl radicals lead to the formation of 8-OH deoxyguanosine, which enhances mutagenesis by converting guanine cytosine base pairs into adenine thymine pairs during deoxyribonucleic acid (DNA) replication.[74–76]

Anticancer activity of major active phytoconstituents of *G. glabra*

Glycyrrhizin

Glycyrrhizin, a triterpenoid saponin in licorice, exhibits anticancer activity by inducing mitochondrial dysfunction, ROS production, caspase activation, and apoptosis in cholangiocarcinoma cells. It also triggers cell cycle arrest and inhibits cervical cancer cell growth by downregulating the Notch pathway, suggesting its potential as a chemopreventive agent.[77,78]

Glycyrrhetinic acid

Glycyrrhetinic acid, a pentacyclic triterpenoid, and its 40 derivatives showed moderate cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cells, with lower effects on normal hTERT-RPE1 cells.[79]

Table 1: Ethanopharmacological profile of *Glycyrrhiza glabra*

Country	Complaints/use	Parts/dosage forms	Method of administration	References
India	Expectorant	*G. glabra* root and rhizome powder used to treat cough, sore throat	Oral	[9]
	Rheumatism, hemorrhagic disease, epilepsy and paralysis	Medicated oil	Topical	[17]
	Cuts and wounds	Powder given with ghee		[17]
	Cough and cold	Root powder with lime juice and linseed	Oral	[17]
	Anemia	Root powder with honey		[18]
	Lactation	*G. glabra* root with cow milk		[19]
	Hoarseness of voice	A confection of rice milk prepared with *G. glabra* root		
	Cardio-tonic	A paste of *G. glabra* root with *Picrorrhiza kurroa* and sugar water		[18]
	Intrinsic tonic	Root paste		[20]
	Graying of hair	Root is used as hair wash	Topical	[9,21]
	Erysipelas	Decoction of *G. glabra*	Oral	
	Edema	Root paste with sesamum indicum		
	Hematemesis	Root with Santalum album and milk		[22]
	Gonorrhea	Bark		[23]
	Hepatitis B	Whole plant		[23]
Pakistan	Infertility in animals like cow, sheep and goat	*G. glabra* root paste with flour and milk	Oral	[24]
Turkey	Manufacturing of wine	Root sap		[25]
Nepal	Stimulator, astringent and tonic	Expressed juice of root and stem		[26]
Egypt	Sore throat	*G. glabra* root/stem powder with tea		[27]
Spain	Common cold	Rhizomes		[28]
South Africa	Ulcer, chest pain Arthritis	Rhizomes	Topical	[29]
Iran	Cold, stomach pain, joint pain	Root and stem		[30,31]

Liquiritin

Liquiritin induces apoptosis in HepG2 cells by disrupting mitochondrial function and regulating proteins like Bcl-2, cytochrome c, and cleaved caspase-3. It also causes G2/M arrest by modulating p21, p27, cyclin B, and CDK1/2. These effects, mediated through the ROS-MAPK/AKT/NF-κB pathway, suggest its potential as a therapeutic agent for hepatocellular carcinoma.[80]

Licochalcones

Licochalcones induce apoptosis and ER stress in carcinoma and sarcoma cells via PI3K/Akt/mammalian target of rapamycin, P53, NF-κB, and P38 pathways, while inhibiting proliferation, migration, invasion, and inflammation.[81]

Glabridin

Glabridin inhibits proliferation in SCC-9 and tongue squamous carcinoma oral cancer cells, inducing sub-G1 arrest, phosphatidylserine externalization, and caspase-mediated apoptosis. It also activates extracellular signal-regulated kinase, p38, and c-Jun N-terminal kinase (JNK) pathways in a dose-dependent manner.[82]

Anti-inflammatory activity of major phytoconstituents of *G. glabra*

Glycyrrhizin

Glycyrrhizin inhibits ROS production by neutrophils, enhances IL-10 in liver dendritic cells, and reduces oxidative stress and inflammation via the Hmgb1/NF-κB pathways. It also boosts antioxidant defense in liver and renal cells by activating the AMP/NRF2 pathway and increasing glutathione-S-transferase activity.[83]

Glycyrrhetinic acid

Oral β-glycyrrhetinic acid inhibits glucocorticoid metabolism by blocking 11β-HSD, enhancing anti-inflammatory effects in skin and lungs. It also prevents complement pathway activation, potentially improving hydrocortisone treatment for inflammatory lung diseases.[84]

Liquiritin

Liquiritigenin inhibits NF-κB activation in macrophages, thereby reducing the production of inducible-nitric oxide synthase and pro-inflammatory cytokines. More

Table 2: List of the major active phytomolecules of *G. glabra* responsible for pharmacological activities

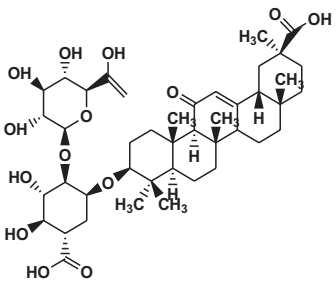
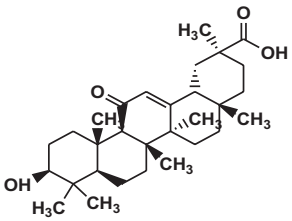
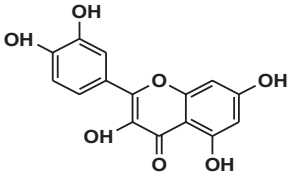
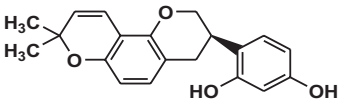
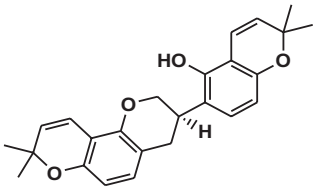
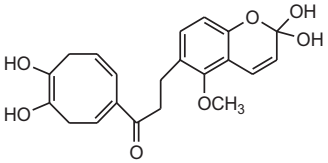
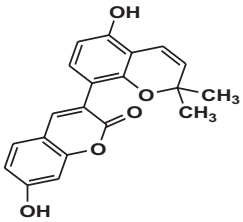
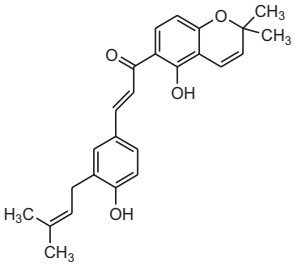
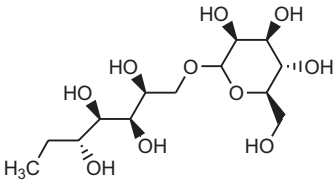
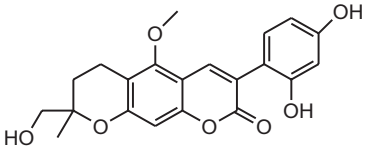
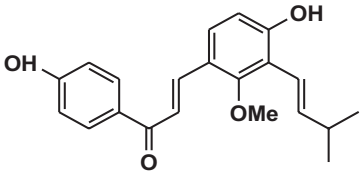
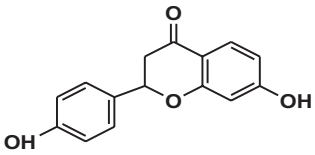
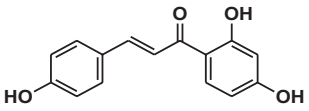
Sr no	Class of secondary metabolites	Isolated phytochemicals	Part/extract	Structure	References
1	Triterpinoid saponin	Glycyrrhizin	Root extract		[32]
2		Glycyrrhinitic acid	Root extract		[33,34]
3	Flavonoids	Querceitin	Root extract		[35]
4	Isoflavones	Glabridin	Ethanolic root extract		[32]
5		Hispaglabridin B	Root extract		[36,37]
6	Chalcone	Glycyglabrone	Root extract		[38,39]
7		Glabracoumarin	Root extract		[40,41]
8		Paratocarpin B	Methanolic root extarct		[36,37]

Table 2. Continued

Sr no	Class of secondary metabolites	Isolated phytochemicals	Part/extract	Structure	References
9	Mannose	Mannopyranosyl-D glucitol	Root extract		[30]
10	Coumarins	Licopyranocoumarins	Methanolic root extract		[40,41]
11	Phenolics	Licochalcones C	Methanolic root extract		[42,43]
12		Liquiritigenin	Root extract		[44]
13		Isoliquiriteginin	Root extract		[45–47]

importantly, it exhibits an anti-edema effect in the carrageenan-induced paw edema model in rats.[85]

Licochalcone A

Licochalcone A inhibits COX-2 synthesis and activity in LPS-induced macrophages, suggesting its potential as a natural COX-2 inhibitor. Other chalcones, like 3,4-dihydroxychalcone, also exhibit COX inhibitory activity, supporting licochalcone A's anti-inflammatory effects.[86]

Glabridin

Glabridin demonstrates anti-nociceptive and anti-inflammatory effects in rat and mouse pain models, reducing reaction times in hotplate and tail flick tests, and decreasing writhing, paw licking, and paw edema. It also lowers pro-inflammatory cytokines, PGE2, and leukocyte migration.[87]

Neuroprotective activity of major phytoconstituents of *G. glabra*

Glabridin

Glabridin-treated mice exhibited elevated acetylcholine levels and a significant reduction in cholinesterase activity in the brain, ultimately leading to improved memory.[88]

Glycyrrhizin

Glycyrrhizin offers neuroprotection by inhibiting HMGB1 activity and reducing pro-inflammatory cytokines, HMGB1 release, and RAGE/TLR4 signaling. It shows potential as a treatment for neurological conditions like traumatic brain injury, neuroinflammation, epilepsy, Alzheimers, Parkinsons, and multiple sclerosis.[89]

Glycyrrhetinic acid

Glycyrrhizic acid and 18β-GA protect PC12 cells from damage by serum/glucose deprivation and 6-OHDA injury, likely through the PI3K/Akt pathway and regulation of mitochondrial Bcl-2 proteins.[90]

Liquiritin

Liquiritin and liquiritin-containing serum protect neuronal cells in a glutamate injury model, delaying apoptosis and reducing cell mortality in BV2 cells. These effects may contribute to its antidepressant activity, though its impact on neuronal morphology is still under investigation.[91]

Licochalcone A

Licochalcone A protects rat cortical neurons from OGD/R-induced damage by reducing oxidative stress

Table 3: Pharmacological activity of *G. glabra* and its major active phytoconstituents on oxidative stress-induced disorders

Name of phytomolecule/ plant extract	Therapeutic effect	Model	Studied dose	Active concentration	Mechanism of action	References
G. glabra extract						
Hydro and methanolic extract	Anticancer	Ehrlich ascites tumor cells (*in vivo* and *in vitro)*	60, 120 μg	Dose-dependent	Cell number Body weight Ascites volume Inhibit tumor cells proliferation	[49]
Aqueous extract	Anti-inflammatory	Acetic acid-induced ulcerative colitis (*in vivo*)	50, 100 and 150 mg/kg	100 and 150 mg	Colonic inflammatory response and edema	[50]
Aqueous extract	Neurodegenerative disorder (dementia)	Scopolamine-induced amnesia (*in vivo*)	75, 150 and 300 mg/kg	150 mg	Inflammatory Improved learning and memory	[51]
Isolated major active phytomolecules of *G. glabra*						
Glycyrrhizin	Anticancer	A549 cells (*in vitro*)	0.25–1.5 mM	1.0 mM	Inhibited the proliferation of A549 lung adenocarcinoma cells and triggered the apoptosis pathway leading to cell death	[52]
Glycyrrhetinic acid	Anticancer	Rh30 cells (*in vitro*)	1 or 5 µmol/L	0.83 mmol/L	Glutathione activity, reactive oxygen species, and down regulated the expression of specificity protein (Sp) transcription factors Sp1, Sp3, and Sp4	[44]
	Anti-inflammatory	Mouse3T3-L1cells (*in vitro*)	1–40 µM	1 µM	Influenced adipogenesis in maturing preadipocytes and induced lipolysis in mature adipocytes	[53]
	Neuroprotective	PC12 cells (*in vitro*)	0.5 mg/mL	0.5 mg/mL	Inhibited apoptosis Mitochondrial Bax/Bcl-2 protein levels Activate the PI3K/Akt pathways	[54]
Liquiritin	Neuroprotective	B65 cells (*in vitro*)	1–100 µM	Dependent on dose	Upregulated the expression of functional glucose-6-phosphate dehydrogenase and antioxidants	48
Isoliquiritin	Cytoprotective	PC12 cells (*in vitro*)	1–20 µmol/L	20 µmol/L	Corticosterone mediated cell damage by decreasing oxidative stress, catalase, and malondialdehyde	[55]
Licochalcone A	Anti-inflammatory	Chondrocytes (*in vitro*)	5–10 µM	Dose-dependent	Suppressed the production of MMP1, MMP3, and MMP13 in chondrocytes stimulated by IL-1β	[56]
	Anticancer	NSCLC cells (*in vitro*)	0–15 µM	15 µM	Induced autophagy Expression of LC3-II protein, which is involved in autophagosome formation	[57]
	Anticancer	MCF-7 cell (*in vitro*)	10–100 µM	50–100 µM	Enhanced LC3-II signaling and suppressed the PI3K/RAC-α serine-threonine-protein kinase (Akt)/mammalian target of rapamycin signaling pathway	[58]
	Anticancer	T24cell (*in vitro*)	0–100 µM	50–100 µM	Triggered the mitochondrial-dependent pathway of apoptosis by activating mitochondrial membrane potential loss, caspase-3, and PARP cleavage	[59]

Table 3. Continued

Name of phytomolecule/ plant extract	Therapeutic effect	Model	Studied dose	Active concentration	Mechanism of action	References
Licochalcone B	Anti-Alzheimer's	SH-SY5Y cells (*in vitro*)	–	2.16 μM	Prevented the aggregation of amyloid beta-protein by blocking salt bridge interactions at the C-terminus	[60]
	Anticancer	A375 and A431 cells (*in vitro*)	5–20 μM	13.7 and 19.1 μM	Initiated both the extrinsic and intrinsic pathways of apoptotic cell death	[61]
	Anticancer	HepG2 cells (*in vitro*)	40–180 μM	110.15 μM	Caused cell death in cancer cells by activating both the receptor and mitochondrial-mediated pathways of apoptosis	[62]
Licochalcone C	Anti-inflammatory	H9C2 cells (*in vitro*)	25 μM	25 μM	Exerted anti-inflammatory effects by reducing NF-κB and other downstream molecules, including inducible-nitric oxide synthase, ICAM-1, VCAM-1, and others	[63]
Licochalcone D	Anti-inflammatory	RAW264.7cells (*in vitro*)	10 μM	10 μM	Blocked the LPS-induced phosphorylation at serine 276 and transcriptional activation of NF-κB	[64]
	Anticancer	HCC827 cells (*in vitro*)	5–20 μM	Dose-dependent	Caused apoptotic cell death by arresting cell cycle progression during the G2/M transition phase	[65]
Glabridin	Anti-inflammatory	Mice (*in vivo*)	10–30 mg/kg	20–30 mg/kg	Anti-inflammatory effect Serum IgE levels, total protein, enhance respiratory function	[66]
	Anticancer	SK-BR-3 cell (*in vitro*)	10–100 μm/L	Dose-dependent	Expression levels of phosphorylated epidermal growth factor receptor (p-EGFR), p-AKT, p-ERK1/2, cyclin D1, and other related proteins	[67]

ERK = extracellular signal-regulated kinase

and inflammation, activating the SIRT1/Nrf2 pathway and inhibiting NF-κB signaling.[92]

Conclusion

This review offers a thorough examination of the phytochemical composition, pharmacological activities of key phytomolecules of "*G. glabra*" Linn., with an emphasis on its antioxidant potential and therapeutic uses in chronic conditions linked to ROS. The findings highlight its significant role in modulating oxidative stress, supported by its diverse phytochemical and bioactive properties. Although substantial progress has been made in understanding these effects, the review emphasizes the need for advanced research to clarify the specific mechanisms behind these biological activities. Despite the increasing evidence, there remains an urgent need for well-designed double-blind randomized controlled trials to confirm the clinical efficacy of "*G. glabra*." Investigating different combinations of licorice preparations across various disorders could provide valuable insights and enhance treatment approaches. Future research should focus on generating empirical data to support the integration of "*G. glabra*" in pharmaceutical applications, ensuring its effective and controlled use in managing conditions related to oxidative stress.

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Author contributions

Contributors to the manuscript are Dhritika Pandey, Vishwesh Dubey, and Anupriya Singh. Dhritika Pandey and Vishwesh Dubey were involved in manuscript writing and investigation. Anupriya Singh contributed

by checking the manuscript and was responsible for the concepts, design, and defining the intellectual content.

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Conflicts of interest
There are no conflicts of interest.

Abbreviations

AKT RAC	Alpha serine/threonine–protein kinase
AR	Allergic rhinitis
Bax	Bcl-2-associated X-protein
BID	BH3 interacting domain death agonist
CCa	Cervical cancer
COX	Cyclooxygenase
ECM	Extracellular matrix
FITC	Fluorescein isothiocyanate
GLY	Glycyrrhizin
GSH	Glutathione
HCC	Human cholangiocarcinoma cell line
HMGB1	High mobility group box 1
hTERT-RPE1	hTERT-immortalized retinal pigment epithelial cells
ICAM-1	Intercellular adhesion molecule-1
IFN-γ	Interferon-gamma
IL-4	Interleukin-4
IL-6	Interleukin-6
iNOS	Inducible-NO synthase
IκB	Inhibitor of nuclear factor-κB
JNK	c-Jun N-terminal kinase
LCA	Licochalcone A
LDL	Low density lipoprotein
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase

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