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Review Article

Chemistry and Pharmacological Properties of Glycyrrhetinic Acid: A Review

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ABSTRACT

In this article, the chemistry and pharmacological properties of glycyrrhetinic acid (GA), a pentacyclic triterpenoid of the oleanane-type from the root of *Glycyrrhiza glabra* (licorice), is reviewed. With a molecular formula of $C_{30}H_{46}O_4$ and a molecular weight of 470.7 g/mol, GA consists of two stereoisomers, namely, 18β-GA and 18α-GA. Major pharmacological properties of GA highlighted are hepatoprotective, neuroprotective, cardioprotective and nephroprotective activities. Other pharmacological properties of GA reviewed include anti-asthmatic, skin protection, anti-methicillin-resistant *Staphylococcus aureus* (MRSA), anti-parasitic, anti-periodontitis, anti-alopecia, anti-osteoclastogenesis, hypolipidemic, lung protection, cell protection, improved pulmonary hypertension, amelioration of gastric mucosal injury, anti-cystitis glandularis, anti-ulcerative colitis and anti-viral activities. Prospects and topics of further research are suggested in the concluding remarks.

Keywords: Pentacyclic Triterpenoid, Hepatoprotective, Neuroprotective, Cardioprotective, Nephroprotective

Introduction

In this article, glycyrrhetinic acid (GA) from the root of *Glycyrrhiza glabra* (licorice) is chosen as the compound for review. After describing the botany of *G. glabra*, the chemistry and pharmacological properties of GA notably hepatoprotective, neuroprotective, cardioprotective, and nephroprotective activities are highlighted. This is followed by description of other pharmacological activities, and concluding remarks on prospects and suggestions for further research of GA. The other pharmacological activities are those that are less often documented. Well-known properties such as anti-cancer and anti-inflammatory activities are not included in this review. *Glycyrrhiza glabra* L. of the family Fabaceae is commonly known as licorice or liquorice.[1-3] The plant is a herbaceous perennial, with stems 0.5–1.5 m in height. Roots of *G. glabra* are stoloniferous. Leaves are pinnate bearing oblong-lanceolate or elliptic leaflets. Upper surfaces of the leaf blades are glabrescent or pilose while lower surfaces are densely scaly and pubescent on veins. Inflorescences of *G. glabra* are racemose with many small flowers bearing petals that are purple or pale blue in color (Figure 1). Fruits are oblong, flat, glabrous or sparsely hairy pods, containing dark green seeds.[1-3] Other *Glycyrrhiza* species prescribed as licorice in the Chinese Pharmacopoeia are *G. uralensis* (flowers are purple, white or yellow) and *G. inflata* (flowers are purple or light purple).[4] In traditional Chinese medicine (TCM), licorice has been used to strengthen the digestive system, eliminate phlegm, relieve coughing and alleviate pain.[4,5] Chinese licorice formulations in the form of solution, tablet, and powder are used to treat inflammatory diseases. Some prescribed to treat bronchitis, colds, cough and respiratory infections have been patented.[6]

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From the roots of *Glycyrrhiza* species (Figure 1), more than 20 triterpenoids and 300 flavonoids have been reported.[4] Most of these compounds possess bioactivities such as antitumor, antimicrobial, antiviral, anti-inflammatory, immunoregulatory, etc. The extract of licorice has been used for the treatment of gastric ulcers, liver diseases, Addison's disease, allergies and many other diseases. Compounds in licorice possessing anti-inflammatory properties include triterpenoids such as GA and glycyrrhizinic acid (glycyrrhizin), and flavonoids such as licochalcones A−E, isoliquiritigenin, dehydroglyasperins C & D, echinatin, glabridin, licoricidin, isoangustone A and licorisoflavan A.[5] Licorice contains bioactive chemical constituents such as triterpenoids, flavonoids, isoflavonoids, stilbenoids and coumarins.[7-9] The triterpenoids are GA, glycyrrhizin, liquiritic acid, and glycyrretol. Flavonoids, include liquirtin, liquiritigenin and neoliquiritin while isoflavonoids are glabridin, glabrone, glyzarin and galbrene. Coumarins are liqcoumarin and umbelliferone, while dihydrostilbenes are stilbenoids.

Figure 1: Flowers (left) and root slices (right) of *Glycyrrhiza glabra* (licorice)

Chemistry

GA, a pentacyclic triterpenoid of the oleanane-type from licorice, has a molecular formula of $C_{30}H_{46}O_4$ and a molecular weight of 470.7 g/mol.[9-11] Pentacyclic triterpenoids are natural compounds that have been extensively studied for their diverse medicinal and

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pharmacological activities. GA is a good candidate for this study. Its chemical structure consists of a hydroxyl (−OH) group at C3, a keto or carbonyl moiety (=O) at C11, and a carboxylic acid (−COOH) group at C30 (Figure 2). The hydroxyl group at C3 is essential for preserving the cytotoxicity of GA. GA consists of 18*β*-GA and 18*α*-GA (Figure 2). These are two stereoisomers and their chemical structures differ in the stereochemical feature at the junction of the D/E rings.[13] 18*β*-GA has a *cis* junction while 18*α*-GA has a *trans* junction at position 18. 18*β*-GA is (3*β*,18*β*)-3-hydroxy-11-oxoolean-12-en-30-oic acid or enoxolone while 18*α*-GA is (3*β*,18*α*)-3-hydroxy-11-oxoolean-12-en-29-oic acid.[14] GA, a triterpenoid aglycone, i.e. without the glycosyl group, is the major bioactive constituent of the root of *G. glabra*.[10,12]
Using the HPTLC densitometric method, the content of GA and glycyrrhizin in the root of *G. glabra* was found to be 0.84% and 1.07%, respectively.[15] Glycyrrhizin with a molecular formula of $C_{42}H_{62}O_{16}$ and a molecular weight of 822.9 g/mol, is the main active compound in licorice root. GA is a derivative of glycyrrhizin formed by gut bacteria *via* hydrolysis. GA from the root of *G. glabra* was quantified as 0.65% using the TLC densitometric method.[16] In the root of *G. uralensis*, the content of GA was reported to be 10.2 mg/g while that of glycyrrhizin was 7.5 times more.[17]

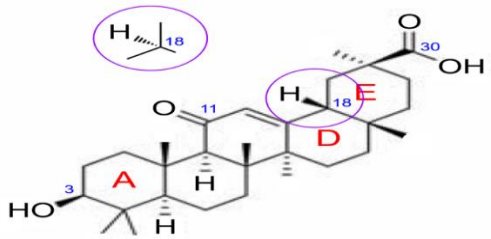

Figure 2: Chemical structure of 18*β*-glycyrrhetinic acid with 18*α*-glycyrrhetinic acid as inset

Pharmacological Properties
Reviews have reported that GA possesses diverse pharmacological propertie.[18-21] Major pharmacological properties being anti-cancer, anti-inflammatory, antibacterial, antiviral and antioxidant effects. In this article, the pharmacological activities and number of studies in brackets of GA reviewed are hepatoprotective (15), neuroprotective (15), cardioprotective (10) and nephroprotective (9) properties. Their activities are tabulated based on their effects, mechanisms and references as shown in Table 1.

Hepatoprotective
In the hepatoprotective studies, GA protected against liver injury and the mechanism involved the inhibition of cytochrome P450 2E1 and its free radical scavenging (FRS) ability; [21] protected against chronic liver fibrosis in mice *via* up-regulation of nuclear factor E2-related protein (Nrf2);[22] protected against chronic liver fibrosis in mice *via* up-regulation of Nrf2;[23] protected against hepatotoxicity in rats *via* peroxisome proliferator-activated receptor gamma (PPARγ) and Nrf2 up-regulation;[24] alleviated toxicity through reversing the fatty acids metabolic pathway;[25] and alleviated hepatotoxicity in rats *via* anti-inflammation, antioxidation and anti-apoptosis.[26] In addition, GA protected against liver injury in rats *via* reduced liver oxidative stress and improved lipid metabolism;[27] protected against cholestatic liver injury in bile duct-ligated rats by restoring the homeostatic regulation of bile acid metabolism, by alleviating oxidative stress, inflammation, and apoptosis, and by impairing autophagy; and fibrosis;[28] protective against cholestatic liver injury *via* choleretic and anti-inflammatory mechanisms involving inhibition of the toll-like receptor 2 (TLR2)/nuclear factor kappa B (NF-κB) pathway and up-regulation of hepatic farnesoid X receptor (FXR) expression;[29] ameliorated hepatic fibrosis by inducing reactive oxygen species (ROS)-mediated apoptosis and targeting PRDX1/2 in activated hepatic stellate cells (HSC);[30] and protected against liver injury *via* alleviation in ferritinophagy and ferropsis followed by improvement in the mitochondrial function.[31] Recent studies have shown that GA protected against liver damage by reducing malondialdehyde levels, mitigating oxidative stress, and ameliorating inflammation;[32] by inhibiting TNF-α/NF-κB/p38-MAPK, JAK1/STAT1 pathways, oxidative stress and apoptosis;[33] by facilitating hepatocyte proliferation and activating the MAPK/Erk signaling pathway;[34] by inhibiting GPX4-dependent ferroptosis;[35] and by bimodal and time-dependent pharmacological activities.[36]

Neuroprotective
Neurological models have been used to assess their effects of GA and its derivatives on ischemia (stroke), Alzheimer's disease (AD) and Parkinson's disease. Among these studies, GA has found to modulate microglia-suppresses experimental autoimmune encephalomyelitis (EAE) in mice by inhibiting microglia activation-mediated central nervous system (CNS) inflammation.[42] Microglia are cells that play an important role in inflammatory demyelination diseases, such as multiple sclerosis. In neuroprotective activities, GA protected PC12 cells from cytotoxicity *via* modulation of the PI3K/Akt pathway;[37] *Yokukansan* (YKS), a traditional Japanese medicine containing GA when fed to rats exhibited neuroprotection. In another study, GA attenuated oxidative and neuronal damage in the brain of mice by increasing antioxidant defense and decreasing lipid peroxidation.[40] GA also attenuated neuronal damage in brain tissue of mice *via* the increase in antioxidant defense and decrease in lipid peroxidation; suppressed experimental allergic encephalomyelitis (EAE) in mice with neurodegenerative effect by inhibiting microglia activation, alleviating inflammation, strengthening antioxidant and promoting remyelination.[42] GA protected Schwann cells with induced injury by reducing reactive oxygen species (ROS) and apoptosis; and protected against neurotoxicity in the brain tissue of rats *via* neuronal apoptosis, endoplasmic reticulum (ER) stress, and Janus kinase 1 (JAK1)/signal transducer and activator of transcription 1 (STAT1) signaling pathway.[45] GA also protected neuronal cells from ferroptosis in mice through inhibition of iron accumulation and up-regulation of coenzyme Q10 (CoQ10) level;[44] exhibited neuroprotection in ischemic stroke of mice through high-mobility group box 1 (HMGB1) inhibition and microglia polarization (MP) regulation;[46] nose-to-brain delivery improved scopolamine-induced memory impairment in rats;[47] and protected against cerebral ischemia/reperfusion (I/R) injury in rats by autophagy and by inhibiting the Janus kinase 2 (JAK2)/STAT3 pathway.[48] GA inhibitory effects on AD involved key signaling pathways, such as toll-like receptor 4 (TLR4), nuclear factor kappa B (NF-κB), mitogen-activated protein kinase, (MAPK) and cholinergic signaling.[49]

Cardioprotective
Model types used to study of the cardioprotective effects of GA include myocardial ischemia-reperfusion[52] and doxorubicin-induced cardiotoxicity.[56] In cardioprotective studies, GA protected the rat heart from ischemia/reperfusion (I/R) injury by attenuating fatal ventricular arrhythmia (FVA) during the reperfusion period, suggesting its antiarrhythmic role;[52] protected H9c2 cells from apoptosis, and oxygen glucose deprivation (OGD)-induced injury *via* the PI3K/Akt signaling pathway;[53] improved cardiac diastolic dysfunction induced by I/R injury by attenuating intracellular calcium overload;[54] protected against myocardial infarction in mice *via* inhibition of apoptosis, inhibition of Ca^{2+} influx, and activation of the PI3K/Akt pathway;[55] protected against cardiotoxicity in H9c2 and AC16 rat cells by suppressing oxidative stress, mitochondrial dysfunction and apoptosis *via* up-regulation of the Nrf2/HO-1 signaling pathway.[56] GA also attenuated global cerebral I/R-induced cardiac damage in mice by amelioration of oxidative and histological damage of heart tissue;[57] protected against chronic heart failure in rats by reducing lipid levels, up-regulating the expression of fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor A (VEGFA), attenuating endothelial nitric oxide synthase (eNOS) expression, and modulating metabolic pathways;[58] protected against cardiotoxicity through anti-apoptotic and antioxidant mechanisms; protected against myocardial I/R injury in mice by exerting anti-inflammation and antioxidant activities;[59,60] and protected against myocardial dysfunction by inhibiting the secretion of angiotensinogen (AGT) by HepG2 cells and by alleviating the elevation of mitochondrial oxidative stress in cardiomyocytes.[61]

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Table 1: Pharmacological activities, effects and mechanisms of glycyrrhetinic acid (GA).

Activity	Effect and mechanism	Reference
Hepatoprotective		
The hepatoprotective effects of GA on CCl4-induced liver injury in mice involved the inhibition of cytochrome P450 2E1 and its FRS ability.		21
GA exerted hepatoprotective activity on CCl_4-induced chronic liver fibrosis in mice by reducing oxidative stress and up-regulating the nuclear translocation of Nrf2.		22
GA protected against CCl_4-induced chronic liver fibrosis in mice *via* up-regulation of Nrf2.		23
GA exerted protective effects against CPA-induced hepatotoxicity in rats *via* PPARγ and Nrf2 up-regulation.		24
The protection of GA towards APAP-induced toxicity was through reversing the fatty acids metabolic pathway.		25
GA protected against TPL - induced hepatotoxicity in rats *via* anti-inflammation, antioxidation and anti-apoptosis.		26
GA protected against CCl_4-induced liver injury in rats *via* reduced liver oxidative stress and improved lipid metabolism.		27
GA protected against cholestatic liver injury in bile duct-ligated rats by restoring the homeostatic regulation of bile acid metabolism, by alleviating oxidative stress, inflammation and apoptosis, and by impairing autophagy and fibrosis.		28
GA exerted hepatoprotective effects on LCA-induced cholestatic liver injury *via* choleretic and anti-inflammatory mechanisms involving inhibition of the TLR2/NF-κB pathway and up-regulation of hepatic FXR expression.		29
GA ameliorate hepatic fibrosis by inducing ROS-mediated apoptosis and targeting PRDX1/2 in activated HSC.		30
GA protected against DON-induced liver injury *via* alleviation in ferritinophagy and ferropsis followed by improvement in mitochondrial function.		31
GA and gallic acid prevented AZM-induced liver damage in rats by reducing malondialdehyde levels, mitigating oxidative stress, and ameliorating inflammation.		32
GA mitigated BPA-induced liver damage by inhibiting TNF-α/NF-κB/p38-MAPK, JAK1/STAT1 pathways, oxidative stress and apoptosis.		33
GA accelerated liver regeneration in mice after partial hepatectomy by facilitating hepatocyte proliferation and activating the MAPK/Erk signaling pathway.		34
GA alleviated DON-induced hepatotoxicity in HepG2 cells and mice by inhibiting GPX4-dependent ferroptosis.		35
GA-albumin nanoparticles restored acute liver injury in mice *via* bimodal and time-dependent pharmacological activities.		36
Neuroprotective		
GA protected PC12 cells from 6-OHDA-induced cytotoxicity *via* modulation of the PI3K/Akt pathway.		37
YKS, a traditional Japanese medicine containing GA, was orally fed to rats and its blood-brain barrier permeability was assessed. Results showed that GA was detected in the plasma, brain and cerebrospinal fluid of rats. It is evident that GA is absorbed into the blood and then reaches the brain through the BBB.		38
Oral administration of YKS to rats showed that specific binding sites for GA existed in the rat brain as 11β-HSD1.		39
GA attenuated oxidative and neuronal damage in brain tissue caused by global cerebral I/R in mice *via* the increase in antioxidant defense and decrease in lipid peroxidation.		40
GA attenuated neuro-inflammation in LPS-induced inflammation neuronal cells of the hippocampus by promoting anti-inflammatory and anti-apoptosis effects.		41
GA suppressed EAE in mice by inhibiting microglia activation, alleviating inflammation and promoting remyelination.		42
GA when fed to *Caenorhabditis elegans* (nematode) had proteasome activation that retarded aging and AD progression.		43
GA protected the brain tissue against EAE in mice with neuro-degenerative effect *via* its antioxidant and anti-inflammatory activities.		44
GA protected against H_2O_2-induced injury in Schwann cells by reducing ROS and apoptosis.		45
GA possessed neuroprotective effects on BPA-induced neurotoxicity in the brain tissue of rats with mechanisms involving neuronal apoptosis, ER stress, and JAK1/STAT1 signaling pathway.		46
GA protected neuronal cells from ferroptosis in mice through inhibition of iron accumulation and up-regulation of CoQ10 level.		47
Polymeric nanoparticles conjugated with GA exhibited neuroprotection in ischemic stroke of mice through HMGB1 inhibition and MP regulation.		48
GA in LNC was fed to rats by intranasal administration. Nose-to-brain delivery of GA improved scopolamine-induced memory impairment in the rats, providing a promising remedy for AD.		49
GA protected against cerebral I/R injury in rats by autophagy and by inhibiting the JAK2/ STAT3 pathway, suggesting its potential as a drug candidate for ischemic stroke.		50
GA inhibited the effects of AD involving key signaling pathways, such as TLR4, NF-κB, MAPK and cholinergic signaling.		51
Cardioprotective		
GA protected the heart from I/R injury by attenuating FVA during the reperfusion period in the rat heart, suggesting it is antiarrhythmic role.		52
GA protected H9c2 cells from apoptosis and OGD-induced injury *via* the PI3K/Akt signaling pathway.		53
GA improved cardiac diastolic dysfunction induced by I/R injury by attenuating intracellular calcium overload.		54
GA protected against myocardial infarction in mice *via* inhibition of apoptosis, inhibition of Ca^{2+} influx, and activation of the PI3K/Akt pathway.		55
GA protected against DOX-induced cardiotoxicity in H9c2 and AC16 cells by suppressing oxidative stress, mitochondrial dysfunction, and apoptosis through up-regulation of the Nrf2/HO-1 signaling pathway.		56
GA attenuated global cerebral I/R-induced cardiac damage in mice by amelioration of oxidative and histological damage of heart tissue.		57
GA and HA protected against chronic heart failure in rats. The mechanisms may involve reducing lipid levels, up-regulating the expression of FGF2 and VEGFA, attenuating eNOS expression and modulating metabolic pathways.		58
GA exerted cardioprotective effects against BPA-induced cardiotoxicity through anti-apoptotic and antioxidant mechanisms, suggesting its role in maintaining cardiac health.		59

Neutrophil‐mediated delivery of GA exerted cardioprotection against myocardial I/R injury in mice by exerting anti-inflammation and antioxidant activities.	60
GA was identified as an AGT inhibitor against LPS-induced myocardial dysfunction. It inhibited the secretion of AGT by HepG2 cells and alleviated the elevation of mitochondrial oxidative stress in cardiomyocytes.	61
Nephroprotective	
GA protected against CP-induced nephrotoxicity in renal cells of mice by up-regulating Nrf2, down-regulation NF-κB, and significantly inhibiting HMGB1 in the kidney.	62
GA protected against MTX-induced nephrotoxicity in the kidney of mice by attenuating oxidative stress and inflammation, and by up-regulating the Nrf2/ARE/HO-1 pathway.	63
GA protected against CP-induced kidney injury in mice by inhibiting apoptosis of renal cells, enhancing BMP-7, and targeting HDAC2.	64
GA ameliorated fructose-induced nephropathy in renal cells of mice by suppressing ROS production, lipid accumulation, and inflammation.	65
GA improved kidney function and alleviated RF in mice by inhibiting the inflammatory response characterized by reduction in the activation and migration of inflammatory cells.	66
GA protected kidney tissue from LPS-induced oxidative and tissue damage based on histopathological and oxidative stress analyses.	67
GA attenuated D-galactose-induced oxidative stress and inflammatory responses in the kidneys of weaned piglets.	68
GA loaded in carthamin yellow liposomes alleviated interstitial fibrosis in diabetic nephropathy.	69

AD = Alzheimer's disease, AGT = angiotensinogen, Akt = protein kinase B, APAP = acetaminophen, ARE = antioxidant response element, AZM = azithromycin, BBB = blood-brain barrier BMP-7 = bone morphogenetic protein-7, BPA = bisphenol A, CCl_4 = carbon tetrachloride, CNS = central nervous system, CoQ10 = coenzyme Q10, CP = cisplatin, CPA = cyclophosphamide, DON = deoxynivalenol, DOX = doxorubicin, EAE = experimental allergic encephalomyelitis, eNOS = endothelial nitric oxide synthase, ER = endoplasmic reticulum, FGF2 = fibroblast growth factor 2, FRS = free radical scavenging, FVA = fatal ventricular arrhythmia, FXR = farnesoid X receptor, GPX4 = glutathione peroxidase 4, HA = hypaconitine, HDAC2 = histone deacetylase 2, HMGB1 = high-mobility group box 1, HO-1 = hemoxygenase-1, H_2O_2 = hydrogen peroxide, HPD = haloperidol, HSC= hepatic stellate cells, 11β-HSD1 = 11β-hydroxysteroid dehydrogenase type-1, I/R = ischemia/reperfusion, JAK = Janus kinase, LCA = lithocholic acid, LNC = lipid nanocapsules, LPS = lipopolysaccharide, MAPK= mitogen-activated protein kinase, MP = microglia polarization, MTX = methotrexate, NB = nose to brain, NF-κB = nuclear factor kappa B, Nrf2 = nuclear factor E2-related protein, OGD = oxygen glucose deprivation, 6-OHDA = 6-hydroxydopamine, PI3K = phosphatidylinositol 3-kinase, PPAR-γ = peroxisome proliferator-activated receptor gamma, PRDX1/2 = peroxiredoxin1/2, RF = renal fibrosis, ROS = reactive oxygen species, STAT = signal transducer and activator of transcription, TLR2 = toll-like receptor 2, TNF-α = tumour necrosis factor, TPL = triptolide, VEGFA = vascular endothelial growth factor A, and YKS = *Yokukansan*.

Nephroprotective

GA protected against nephrotoxicity in renal cells of mice by up-regulating nuclear factor E2-related protein (Nrf2), down-regulating NF-κB, and significantly inhibiting HMGB1 in the kidney;[62] protected against nephrotoxicity in the kidney of mice by attenuating oxidative stress and inflammation, and by up-regulating the Nrf2/ARE/HO-1 pathway;[63] and protected against CP-induced kidney injury in mice by inhibiting apoptosis of renal cells, promoting bone morphogenetic protein-7 (BMP-7), and targeting histone deacetylase 2 (HDAC2).[64]

Also, GA ameliorated nephropathy in renal cells of mice by suppressing ROS production, lipid accumulation, and inflammation;[65] improved kidney function and alleviated renal fibrosis (RF) in mice by inhibiting the inflammatory, and by reduction in the activation and migration of inflammatory cells;[66] and protected kidney tissue from oxidative and tissue damage based on histopathological and oxidative stress analyses.[67] Recent studies have reported the GA protected against kidney damage by attenuating D-galactose-induced oxidative stress and inflammatory responses.[68] and by alleviating interstitial fibrosis.[69]

Other Properties

Apart from anti-cancer and anti-inflammatory activities of GA, other pharmacological properties include anti-asthmatic, skin protection, antibacterial, anti-parasitic, anti-periodontitis, anti-alopecia, anti-osteoclastogenesis, anti-obesity, pulmonary hypertension, anti-cystitis glandularis, anti-ulcerative colitis and anti-viral activities.

Anti-asthmatic

GA exhibited a regulating effect on bronchial asthma (BA) smooth muscle proliferation and apoptosis including inflammatory factor expression in guinea pigs *via* the extracellular signal-regulated kinase (ERK)1/2 signaling pathway.[71] GA significantly inhibited ovalbumin (OVA)-induced airway inflammation, eosinophil infiltration and airway hyper-responsiveness (AHR) in a mouse model of allergic asthma by suppression of Th2 cytokines *via* signal transducer and activator of transcription 6 (STAT6), GATA-binding protein 3 (GATA-3) and fork-head box p3 (Foxp3) transcription pathways.[72] These data suggested that GA is a novel therapeutic compound for the treatment of inflammatory airway disorders, including allergic asthma. GA suppressed allergic airway inflammation in asthma mice through nuclear factor kappa B (NF-κB) and nuclear factor erythroid 2-related factor-2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathways.[72]

Skin protection

GA has been reported to possess skin protection effects on mice with experimental skin damage. Against ultraviolet (UV) irradiation-induced skin photoaging in mice, the protective effect of GA was mainly attributed to its antioxidative and anti-inflammatory properties, as well as the significantly inhibition of the expression of matrix metalloproteinase (MMP)-1 and -3.[73] GA promoted the proliferation, migration, and aquaporin-3 (AQP-3) expression of human dermal fibroblast, that implied its role in the treatment of skin diseases characterized by impaired wound healing or dermal defects.[74] GA mitigated radiation-induced skin damage in mice by inhibiting *via* NADPH oxidase-derived ROS production and by activating p38MAPK and NF-κB pathways.[75] GA is a useful remedy for other skin disorders such as atopic dermatitis, hyper-pigmentation and acne.[76] Against imiquimod (IMQ)-induced psoriasis, a chronic skin disease, GA displayed inhibitive effect by breaking CCL20 or CCR6 and targeting glucuronidase beta (GUSB)/activating transcription factor 2 (ATF2) signaling.[77]

Anti-MRSA

GA did not inhibit the growth of *Staphylococcus aureus*, but the secretion of αH by *S. aureus* was significantly inhibited by GA.[78] *In vivo* data showed that GA provided protection against staphylococcal pneumonia in mice by marked alleviating pulmonary inflammation. GA at concentrations exceeding 0.22 μM exhibited bactericidal activity against methicillin-resistant *S. aureus* (MRSA).[79] Topical GA significantly reduced skin lesion and attenuated virulence gene expression in MRSA infected mice. GA exhibited strong antibacterial activity against *S. aureus* including MRSA.[80] This activity might be due to the inhibition of several pathways involved in carbohydrate and amino acid metabolism. GA induced metabolic changes in *S. aureus* and reduced bacterial cell-to-cell interactions.[81]

Anti-parasitic
In vitro studies showed that GA has a IC_{50} value of 1.69 μg/ml against *Plasmodium falciparum*, the parasite of malaria.[82] In malaria infected mice, GA displayed a dose-dependent anti-malarial activity ranging from 68–100% at doses of 62.5–250 mg/kg on day eight. Against microfilariae worms of *Brugia malayi*, the parasite that spreads filariasis, the IC_{50} inhibition of GA was 1.20 μM.[83] However, GA was inactive against adult worms of *B. malayi*. GA displayed anti-leishmanial effect against mice infected with *Leishmania donovani* promastigotes, the parasite of leishmaniasis.[84]

Anti-periodontitis
GA suppressed periodontitis in interleukin-10-deficient mice by inhibiting pro-inflammatory cytokine production and osteoclastogenesis *via* inactivation of nuclear factor-κB.[85] Topical application of GA in the gingival sulcus inhibited attachment loss and alveolar bone resorption in lipopolysaccharide (LPS)-induced experimental periodontitis of rats.[86] GA alleviated oxidative damage in periodontal tissue of rats by modulating the interaction of Cx43 and C-Jun N-terminal kinase (JNK) /nuclear factor kappa-B (NF-κB) pathways.[87]

Anti-alopecia
In a study on the protective effect of GA in male rats with androgen-induced alopecia. Rats with GA applied to the dorsal denuded skin showed excellent hair growth promoting and restoring activity.[88] GA stimulated the proliferation of dermal papilla cells and outer root sheath cells isolated from human hair follicles, suggesting that GA could be a effective treatment for androgenetic alopecia.[89]

Anti-osteoclastogenesis
GA inhibited osteoclastogenesis and bone loss in mice by blocking receptor activator of nuclear factor κB ligand (RANKL)-mediated RANK–TNF receptor-associated factor (TRAF6) interactions, and nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways.[90] GA inhibited interleukin-1β (IL-1β)-induced inflammatory response in mouse chondrocytes and prevented osteoarthritic progression by activating nuclear factor erythroid-derived 2-like 2 (Nrf2).[91]

Hypolipidemic
GA exerted hypolipidemic activity on streptozotocin (STZ)-induced diabetic rats by significantly decreasing plasma high density lipoprotein (HDL)-cholesterol.[92] GA inhibited lipid accumulation during the differentiation of 3T3-L1 preadipocytes and promoted lipolysis in differentiated adipocytes.[93] GA attenuated anandamide (ANA)-induced mouse 3T3-L1 preadipocytes adiposity and high-fat diet (HFD)-induced obese mice.[94]

Lung protection
GA ameliorated idiopathic pulmonary fibrosis (IPF), a lung disease, by modulating the transforming growth factor-β (TGF-β1)/Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway.[95] Against another lung disease, GA reduced lung inflammation caused by *Streptococcus pneumoniae* infection by reducing the toxicity of pneumolysin, a toxin of the bacteria.[96] GA protected against lung injury caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by activating the cyclic GMP-AMP synthase (cGAS)-human stimulator of interferon genes (STING) signaling pathway.[97]

Cell protection
Against H_2O_2-induced oxidative stress in porcine intestinal epithelial cells, GA attenuated oxidative damage and apoptosis *via* activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway.[98]

Alleviation of pulmonary hypertension
GA alleviated pulmonary hypertension in rats by regulating the vascular non-inflammatory molecule-1/L-arginine/nitric oxide signaling pathway.[99]

Amelioration of gastric mucosal injury
GA ameliorated gastric mucosal injury in rats by modulating gut microbiota and its metabolites *via* Thbs1/PI3K-Akt/p53 pathway.[100]

Anti-cystitis glandularis
GA possessed anti-cystitis glandularis effects on mice. GA-treated mice exhibited reduced contents of inflammatory cytokine and down-regulated PTGS2 and MUC1 mRNA, and protein levels.[101]

Anti-ulcerative colitis
GA protected colonic epithelium in ulcerative colitis by activating Wnt/β-catenin pathway to restore tight junction.[102] In the amelioration of ulcerative colitis by GA, meachanism involved modulation of the PPAR-γ/NF-κB signaling pathway.[103]
Anti-viral
GA has a wide range of antiviral activities. Noteworthy are viruses, such as hepatitis virus, herpes virus and coronavirus 2 (SARS-CoV-2).[104]

Conclusion
GA is a pentacyclic triterpenoid from licorice (*Glycyrrhiza glabra*), a useful and multi-purpose medicinal plant. With a molecular formula of $C_{30}H_{46}O_4$ and a molecular weight of 470.7 g/mol, GA consists of two stereoisomers, namely, 18β-GA and 18α-GA. Pharmacological properties of GA reviewed are hepatoprotective, neuroprotective, cardioprotective and nephroprotective activities. Other pharmacological properties include anti-asthmatic, skin protection, antibacterial, anti-parasitic, anti-periodontitis, anti-alopecia, anti-osteoclastogenesis, anti-obesity, pulmonary hypertension amelioration, anti-cystitis glandularis, anti-ulcerative colitis and anti-viral activities. Current evidence on the pharmacology of GA is limited to pre-clinical studies, with a lack of clinical validation. The molecular mechanisms involving the NF-κB and Nrf2 pathways recur in most systems of GA. Research gaps in GA and its derivatives include pharmacokinetics, structure–activity relationship (SAR), toxicology and synergistic formulations. Prospects and topics of further research are suggested in the concluding remarks. Suggestions for further studies of GA include: 1) Chemical modifications of GA aimed at enhancing its potency; More in-depth investigations on the effects and mechanisms with regard to the other pharmacological activities of GA; A comparison between the pharmacological properties of GA and other pentacyclic triterpenoids from *Glycyrrhiza* species such as glycyrrhizin would be interesting to natural product chemists; The dermatological application and drug delivery system of GA are worth of further studies; The development of GA and its derivatives in value-added commercial products, by itself or in combination with other drugs, would attract the exploratory attention of pharmaceutical companies; and Microbiologists would be keen to find out a complete list of bacteria and virus that are susceptible to GA. Overall, the prospects for research and development of GA are promising.

Conflict of Interest
The authors declare no conflict of interest.

Authors' Declaration
The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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