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Review

Unlocking the hidden health benefits of guggulsterone isolated from ancient spices: a comprehensive review

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ABSTRACT

Guggulsterone (GS) is a bioactive compound primarily extracted from the oleo-gum resin of plants in the *Commiphora* and *Boswellia* genera. Modern pharmacological studies have demonstrated that GS possesses a broad spectrum of biological activities, with notable therapeutic potential in inflammatory disorders, neurodegenerative conditions, diabetes mellitus, and various cancers. In this review, we systematically analyzed relevant literature published up to 2024 from the CNKI, Web of Science, ScienceDirect, and PubMed databases to summarize the current understanding of GS's pharmacological effects, toxicity profile, and pharmacokinetic properties. The findings indicate that GS exerts potent antioxidant, anti-inflammatory, anticancer, antiviral, antidepressant, lipid-lowering, and cardiovascular protective effects, primarily through modulation of key signaling pathways such as the Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3), nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1), Nrf2/Keap1, nuclear factor kappa-B (NF-κB), AMPK, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), and mitogen-activated protein kinase (MAPK)/activator protein-1 (AP-1). Additionally, GS may help overcome limitations associated with conventional chemotherapy by modulating drug resistance *via* regulation of p-glycoprotein activity. Following hepatic metabolism mediated by cytochrome P450 enzymes, GS does not appear to cause significant adverse effects. This review provides a comprehensive synthesis of the sources, pharmacological actions, safety, pharmacokinetics, and potential applications of GS. Future research should focus on structural modification of GS, development of novel formulations, and exploration of synergistic combinations with other therapeutic agents to broaden its clinical utility.

1. Introduction

Guggulsterone (GS) is a naturally occurring bioactive compound found in the resin of the *Commiphora* plant. With a chemical formula of $C_{21}H_{28}O_2$ and a molecular weight of 312.49, it exists as a pale-yellow powder and remains stable within the temperature range of 2 to 8 ℃. There are two isomeric forms: *E*-GS [4,17(20)-(*cis*)-pregnadiene-3,16-dione] and *Z*-GS [4,17(20)-(*trans*)-pregnadiene-3,16-dione] [1]. GS is primarily obtained from the dried resin of trees belonging to the Burseraceae family, such as *Commiphora myrrha* and *Commiphora molmol* [2]. Historically, this resin has been used for thousands of years to treat various ailments, including arthritis, inflammation, obesity, cardiac conditions, ulcers, ischemia, epilepsy, and lipid metabolism disorders. Ayurvedic medical works, especially the *Sushruta Samhita*, have indicated that oral GS has proven to be effective in the treatment of various disorders, which include obesity, liver diseases, internal tumors, malignant ulcers, urinary tract ailments, intestinal fistulas, intestinal worms, vitiligo, sinusitis, edema, and sudden paralysis attacks [3].

GS is a lipid-lowering antagonist of the FXR (farnesoid X receptor). Several studies suggest that GS lowers the concentration of several inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). In addition, it reduces the production of free radicals, thus shielding cells against the damage caused by oxidative stress [4]. The underlying mechanisms through which these effects are mediated include the activation of peroxisome proliferator-activated receptors (PPARs) and inhibition of nuclear factor kappa-B (NF-κB) among others. Moreover, GS suppresses proliferation, metastasis, and invasion of certain cancer cells and induces apoptosis. Its anticancer, anti-

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diabetic, and neuroprotective actions have been attributed to its modulation of major signaling pathways, including protein kinase B (Akt) and extracellular signal-regulated kinases (ERK1/2), the Akt-NF-κB pathway, the cAMP-response element binding protein (CREB)-brain-derived neurotrophic factor (BDNF) pathway, the vascular endothelial growth factor (VEGF) pathway, the intrinsic mitochondrial apoptosis pathway, and the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. Therefore, GS is of paramount significance in the prevention and treatment of cancer, diabetes, Alzheimer's disease (AD), and atherosclerosis [4, 5]. It is worth noting that GS, being a natural plant-based compound, can not only provide an alternative to synthetic drugs where its use would be safe and effective in treating the diverse pathological conditions but also has the potential of synergistic action with conventional therapies to help overcome drug resistance. The optimal dosing of GS can be used to effectively balance between efficacy and safety of treatment and reduce local adverse reactions.

The existing studies on the GS have mostly centered on the antineoplastic nature of the drug, but the non-antitumor pharmacological action of the drug has been given a comparatively little attention. hus, this paper will fill this gap by providing a thorough literature review of variables like "GS", "pharmacological effects", "reaction mechanism", "pharmacokinetics", and "safety" in databases, such as PubMed, Web of Science, Science Direct, and CNKI. The search, organization, and summarization of relevant literature up to 2024 were conducted systematically, to present a theoretical background and direction to future studies and clinical use of GS.

2. Source of GS

2.1. Plant extraction

GS is a steroidal compound derived from the oleo-gum resin of plants in the *Commiphora* and *Boswellia* genera [6]. The resin is a complex mixture containing gum, minerals, essential oils, terpenes, sterols, esters, flavonoids, and steroids. GS extraction involves a multi-step process. Guggul resin is first extracted with ethyl acetate to isolate lipid components. Subsequently, pH-gradient fractionation yields approximately 95% neutral, 4% acidic, and 1% alkaline fractions. Further purification of the neutral fraction results in a ketone-rich extract containing about 12% GS, comprising both *E*-(*cis*-) and *Z*-(*trans*-) GS [7, 8]. The reported GS content in myrrh is approximately 2%, although yield varies depending on factors such as plant growth environment, resin collection season, and plant age [9]. GS is predominantly localized in stems, with *E*-GS concentrations ranging from 120.82 to 487.45 $\mu g \cdot g^{-1}$ and *Z*-GS from 111.74 to 487.68 $\mu g \cdot g^{-1}$. Trace amounts are also present in leaves and roots [10].

2.2. Biotechnology and chemical synthesis

Biotechnological and chemical methods offer alternative routes for GS production (Fig. 1). For example, cell cultures of *C. wightii* established in shake flasks or stirred-tank bioreactors can produce GS. After 15 days, the ratio of *E*- to *Z*-isomers reaches approximately 4∶1, with optimal GS production achieved using a 10% (*V*/*V*) inoculum [11]. Alternatively, GS can be synthesized chemically using simple ketones as starting materials. One approach uses 3,16-dipra for acetic acid 16-dehydrogenation of pentenolone; however, this method yields low output and is unsuitable for industrial-scale production [12]. To improve efficiency, *E*-GS has been selectively synthesized from 16,17-epoxy pregnenolone ketone, with observations indicating that *E*-GS can isomerize to *Z*-GS under light, heat, or acid catalysis [13]. More recently, a novel synthetic strategy has been developed using androsterone-3,17-dione as a precursor, involving A-ring protection, region-selective Wittig reaction, and C-16 oxidation to enhance yield and stereoselectivity [14]. An even more efficient method has emerged, utilizing α-silyl carbon positioning to regulate enoic acid transposition, enabling high-yield GS synthesis through a concise synthetic sequence [15].

In summary, researchers are actively developing more efficient, cost-effective, and environmentally sustainable methods for GS production *via* biotechnology and chemical synthesis to meet growing demand.

3. Pharmacological properties of GS

3.1. Anticancer

GS, a bioactive compound derived from natural sources, has shown considerable potential in recent studies for treating lung,

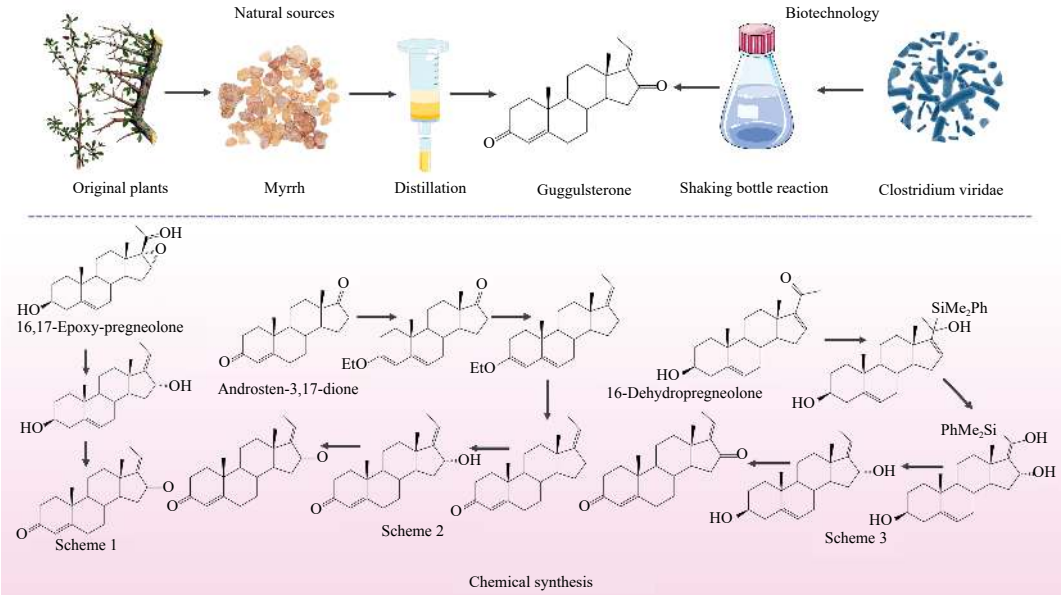

Fig. 1 Main source of the GS.

pancreatic, breast, liver, colorectal, prostate, and head and neck cancers. These investigations consistently report minimal or no toxicity of GS toward normal cells [16]. Multiple mechanisms underlie its anticancer effects (Fig. 2), including induction of apoptosis, cell cycle arrest, and suppression of cancer cell proliferation, migration, angiogenesis, and metastasis [17]. Notably, GS demonstrates significant anticancer activity across diverse cancer types.

3.1.1. Lung cancer

GS exerts inhibitory effects on lung cancer by modulating FXR levels and activating the Akt and ERK1/2 signaling pathways. As an FXR inhibitor, GS downregulates endogenous FXR expression in NSCLC (non-small cell lung cancer) cell lines (A549 and H1975), leading to reduced expression of the downstream effector cyclin D1 and subsequent inhibition of cancer cell proliferation [18]. Western blot analysis of GS-treated NSCLC cells revealed decreased protein levels of cell cycle regulators, including cyclin D1, CDK2, CDK4, CDK6, and phosphorylated Rb (retinoblastoma) protein, suggesting that GS induces G_0/G_1 phase cell cycle arrest and apoptotic cell death. Moreover, there was a negative relationship between the expressions of FXR and programmed death ligand 1 (PD-L1) in a group of 408 samples from NSCLC patients, which suggested the possibility of FXR reversing the PD-L1 overexpression through FXR inhibition [19]. GS inhibits viability/cell cycle development in NSCLC cells and tumor growth in Lewis lung carcinoma (LLC) mouse models. Specifically, 48-h *Z*-GS treatment with 40 μmol·L^{-1} *Z*-GS decreased the LLC cell viability by 44.2%. The flow cytometry revealed that *Z*-GS dose- and time-dependently promoted surface expression of *PD-L1* messenger ribonucleic acid (mRNA) in NSCLC cells [20]. *Z*-GS was found to inhibit the growth of tumors significantly in C57BL/6 mice with subcutaneous LLC tumors. Mechanistically, it partially suppresses FXR and activates Akt and ERK1/2 signaling, leading to an increase in PD-L1 expression *in vivo* and tumor cell proliferation inhibition. *Z*-GS promotes PD-L1 expression in tumor cells, which may counteract its overexpression in NSCLC. Moreover, GS is a PAPSS1 (3'-phosphoadenosine-5'-phosphosulfate synthase 1) inhibitor that binds with a high specificity and affinity to its ATP-binding pocket, enhancing structural stability and reducing conformational flexibility [21]. Recent evidence indicates that *Z*-GS is a potent suppressor of FXR, IL-6, IL6ST, and p-STAT3 expression in mouse models and essentially inhibits tumor migration, invasion, and angiogenesis through JAK2/STAT3 inhibition, thereby providing therapeutic benefits in highly metastatic NSCLC [22]. These results indicate that GS has potential as a therapeutic agent against NSCLC with similar efficacy as other chemotherapy agents, such as paclitaxel, radiation therapy, and targeted drugs or cancer vaccines [23-26], making it an option in the treatment of NSCLC in the future.

3.1.2. Breast cancer

GS prevents breast cancer by interfering with various signaling pathways, such as inhibitor of kappa B kinase (IKK)/NF-κB, mitogen-activated protein kinase (MAPK)/activator protein-1 (AP-1), β-catenin, and p53/cyclin B1 (CCNB1)/Polo-like kinase 1 (PLK1). In the 12-*O*-tetradecanoyl phorbol-13-acetate (TPA)-induced Michigan Cancer Foundation-7 (MCF-7) cells, when treated with 20 μmol·L^{-1} GS, the *cis* isomer decreased cell invasion by 67%, whereas the *trans* isomer reduced it by 51%. Western blot, real-time polymerase chain reaction (RT-PCR), and zymography analyses revealed that the two isomers had a significant effect in inhibiting matrix metalloproteinase (MMP)-9 expression and its upstream regulatory pathways [27]. The mechanisms of action between the isomers are different: *cis*-GS suppresses the IKK/NF-κB pathway through the inhibition of TPA-induced nuclear translocation of p65/p50 and the activity of NF-κB subunits, deoxyribonucleic acid (DNA) binding, and phosphorylation of inhibitor kappa B alpha (IKKαβ and IκBα). Conversely, *trans*-GS inhibits the MAPK/AP-1 pathway through decreasing phosphorylation of ERK, c-Jun *N*-terminal kinase (JNK), and p38 caused by TPA, and preventing the binding activity of AP-1. Both isomers are additive, with a maximum inhibition rate of 79% on MCF-7 cell invasion. Guggulipid, with GS as its primary active component, also affects the β-catenin pathway and induces apoptosis in MCF-7 and MDA-MB-231 breast cancer cells [28]. GS treatment increases cytoplasmic DNA fragmentation and caspase-3 activity while downregulating β-catenin and downstream Wnt/β-catenin effectors. It disrupts β-catenin/TCF-4 (transcription factor 4) binding, inhibits its nuclear translocation of β-catenin, and reduces TCF-4 expression, thereby promoting apoptosis. The anticancer effects of GS

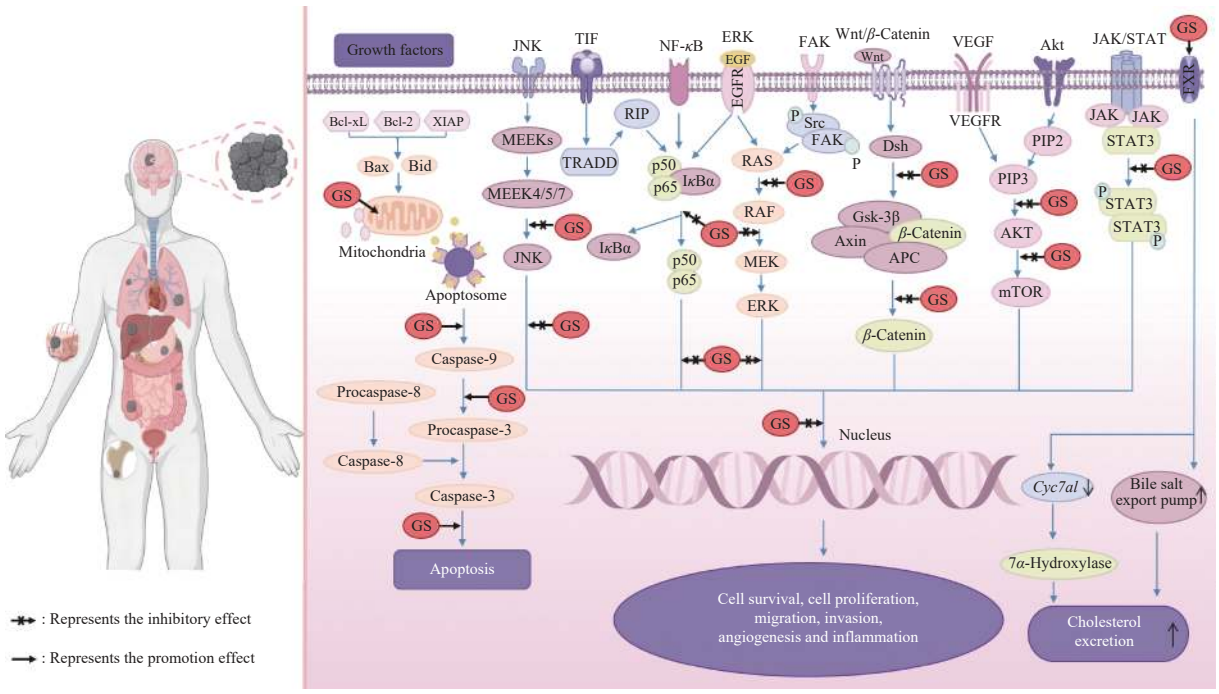

Fig. 2 The anticancer molecular mechanism of GS.

are further attributed to inhibition of DNA methyltransferase activity. Notably, GS reduces DNMT1 (DNA methyltransferase 1), HDAC1 (histone deacetylase 1), and MeCP2 (methyl CpG binding protein 2) protein levels, suggesting epigenetic gene silencing in breast cancer cells [29]. Furthermore, *Z*-GS suppresses the growth of triple-negative breast cancer (TNBC) cell lines through the p53 pathway, leading to cell cycle arrest at G_2/M phase and apoptosis [30]. In preclinical research, *Z*-GS reduces C-X-C motif chemokine receptor 4 (CXCR4) expression in TNBC cells at protein and mRNA levels and decreases transcriptional activity of NF-κB, which inhibits tumor growth [31]. Moreover, *Z*-GS can prevent bone metastasis and lower the concentrations of bone markers including osteopontin (OPN), osteocalcin (OC), and bone sialoprotein (BSP) [32].

These results further our knowledge on GS, but more clinical investigation is required to identify the extent to which GS can influence gene transcription and fully exploit its potential as a candidate drug to prevent the invasion and metastasis of breast tumors.

3.1.3. Liver cancer

The efficacy of GS in treating and preventing liver cancer is linked to its modulation of endoplasmic reticulum stress and the intrinsic mitochondrial apoptosis pathway. Studies show that GS induces endoplasmic reticulum stress and promotes apoptosis in liver cancer cells *via* the PERK (protein kinase R-like endoplasmic reticulum kinase)/eIF2α (eukaryotic initiation factor-2α phosphorylation) pathway, leading to upregulation of CHOP (C/EBP homologous protein) and DR5 (death receptor 5) [33]. In Hep3B cells stained with ER-tracker (FITC dye), GS induced endoplasmic reticulum stress, accompanied by calcium ion release. GS also triggered the unfolded protein response in Hep3B (hepatoma 3B) cells, increasing expression of IRE (inositol-requiring enzyme), JNK, BiP, PERK, eIF2α, and ATF4, ultimately leading to apoptosis. Fluorescence microscopy revealed increased superoxide radicals and hydrogen peroxide levels, along with enhanced DR5 expression and TRAIL-dependent apoptosis. In a study evaluating anti-hepatocellular carcinoma (anti-HCC) activity of the traditional Tibetan medicine DuK (Dawa-ul-Kurkum), molecular docking, MD (molecular dynamics) simulations, and *in vitro* experiments assessed *Z*-GS binding affinities with HCC proteins [34]. Results indicated strong hydrogen bonding interactions (≥ −1.1 kcal·mol^{-1}) between *Z*-GS and cyclin E1, transgelin, ezrin, Rb1, and aminoacylase 1. *Z*-GS exhibited dose-dependent inhibition of clonogenic formation in HuH-7 (human hepatoma-derived-7) cells, reducing colony growth by over 20% at IC_{30} and exceeding 47% at IC_{40}. At IC_{50}, cell density dropped to 19% of control levels. qRT-PCR (quantitative RT-PCR) analysis showed significant upregulation of aminoacylase 1 and RB1, while ezrin and calreticulin were downregulated. Furthermore, *Z*-GS induces apoptosis in human liver cancer cells *via* the intrinsic mitochondrial pathway [17]. Treatment of HepG2 cells with *Z*-GS (5–100 μmol·L^{-1}) caused G_0/G_1 phase arrest and dose-dependent growth inhibition. At 50 and 75 μmol·L^{-1}, apoptotic cells accounted for 24.91% ± 2.41% and 53.03% ± 2.28%, respectively. *Z*-GS significantly increased Bax (Bcl-2-associated X) mRNA and protein expression while decreasing Bcl-2 levels. Enzyme-linked immunosorbent assay (ELISA) revealed reduced TGF-β1 (transforming growth factor β1) and VEGF levels, with increased TNF-α, indicating roles in regulating apoptosis, growth, and metastasis of liver cancer cells.

However, current liver cancer research is limited to *in vitro* studies, lacking animal and clinical trial data. Future investigations are necessary to confirm the safety and efficacy of GS in liver cancer therapy.

3.1.4. Colorectal cancer

Preclinical studies demonstrate that GS treats colorectal cancer by modulating the VEGF pathway and the intrinsic mitochondrial apoptosis pathway. Human colorectal cancer progression depends heavily on angiogenesis, particularly through VEGF [35]. Recent evidence shows that GS inhibits angiogenesis and suppresses tumor development by targeting VEGF. In hypoxic HT-29 cells, treatment with 50 μmol·L^{-1} GS for 48 h reduced cell viability by 50% compared to DMSO controls. Angiogenesis-related downstream proteins, including VEGF, STAT3, and aryl hydrocarbon receptor nuclear translocator (ARNT), were downregulated [36]. Gelatin zymography and qRT-PCR revealed that MMP-2 and MMP-9 expression decreases under hypoxia, suppressing tube formation and migration of human umbilical vein endothelial cells by GS. According to these findings, one of the main targets is the STAT3/hypoxia-inducible factor-1 (HIF-1) pathway, which is associated with the expression of VEGF. A different study established that exposure of HT-29 cells to 50 μmol·L^{-1} GS over 72 h reduced viability by 70% and induced nuclear fragmentation. The possible molecular mechanism is the activation of the mitochondrial pathway and caspase-3, which results in the downregulation of cellular inhibitor of apoptosis protein (cIAP) family members cIAP-1 and cIAP-2 [37]. GS also triggers the extrinsic apoptotic pathway, which involves raising factor-related apoptosis (Fas) protein expression, recruiting Fas-associated death domain protein, and triggering caspase-8 activation. In HT-29 xenograft mouse models, GS (40 mg·kg^{-1}) decreased the mean tumor volume by 78% in HT-29 xenograft mouse models compared with controls. Detection of Bcl-2 in tumor sections by immunohistochemistry revealed the *in vivo* tumor growth inhibition and the induction of apoptosis. A recent proteomic study identified GS as a key inhibitor of human colorectal cancer cell growth [38]. In HCT116 cells, GS altered Bcl-2 expression, promoting cytochrome C release and caspase-3/7 activation *via* the intrinsic pathway. Downregulation of Bcl-2, cIAP-1, and *survivin* (an NF-κB target gene) led to suppressed proliferation, migration, and NF-κB signaling. These results support GS as a promising therapeutic agent for colorectal cancer.

3.1.5. Head and neck cancer

In head and neck cancer, GS shows potential as an inhibitor of ST (smokeless tobacco) and nicotine-induced HNSCC (head and neck squamous cell carcinoma). It acts through multiple pathways, including PI3K (phosphoinositide 3-kinase)/Akt, NF-κB, and STAT3. Studies show that GS treatment inhibits cell growth, induces G_0/G_1 phase arrest, and reduces invasiveness in UM-22b and 1483 cells, as confirmed by flow cytometry [39]. After 24 h, invasive cell numbers decreased by 56.8%. Treatment for 48 h reduced HIF-1 levels in both cell lines, thereby suppressing HNSCC invasion. Oral administration of GS in HNSCC xenografts models decreased total STAT3 expression by 87.3% in UM-22b-derived tumors and 44.3% in 1483-derived tumors, which helped limit tumor growth. GS also impairs the NF-κB pathway in HNSCC, limiting the accumulation of STAT3 and downstream targets like cyclooxygenase-2 (COX-2) and VEGF, which leads to a reduction of inflammation, angiogenesis, and disease progression [40]. Molecular analyses indicate that GS-induced apoptosis is mediated through activation of protein phosphatase 2A that liberates 14-3-3ζ and prevents HNSCC proliferation [41]. GS suppresses the antiapoptotic proteins, including Bcl-2, xIAP, myeloid cell leukemia-1 (Mcl-1), survivin, cyclin D1, and c-Myc, to induce apoptosis. Recent investigations suggest that GS antagonizes ST/nicotine action in the PI3K/Akt pathway [42]. GS prevents phosphorylation of Akt, 3-phosphoinositide-dependent protein kinase-1 (PDK1), and the PI3K p85 subunit in SCC4 cells, suppressing phosphorylation of downstream targets, glycogen synthase kinase-3β (GSK-3β), pRaf, and pS6. As ST and nicotine nor-

mally hyperphosphorylate these targets, GS compensates impaired pro-apoptotic functions of Bax and Bcl-xL/Bcl-2-associated death promoter (Bad) by dephosphorylation of the proteins through the mitochondrial pathway by the protein phosphatase, inhibiting tumor proliferation, metastasis and transformation [43].

The results summarized above provide a strong biological foundation to discuss the clinical applicability of GS as an adjunctive or chemopreventive agent in cancer treatment (Table S1).

3.1.6. Reversing multidrug resistance (MDR)

MDR is one of the most significant cancer treatment challenges. P-glycoprotein (P-gp), a 170-kDa efflux pump, is often overexpressed in tumor cells and is a drug resistance mechanism [44]. Nonetheless, it has been demonstrated that GS can control P-gp and reverse MDR, sensitizing cancer cells to chemotherapeutic drugs. It is highly effective in reversing resistance to drugs like doxorubicin [45]. The flow cytometric analysis of the fluorescence intensity of rhodamine 123 (Rh123) of cells and P-gp expression identified that 100 μmol·L^{-1} GS inhibits the expression and transport activities of P-gp in a dose-dependent manner, which increases intracellular levels of doxorubicin and sensitivity in K562/DOX human myeloid leukemia cells. Doxorubicin resistance is also reversed by GS in MCF-7/DOX breast cancer cells [46]. It is a P-gp substrate, which activates ATPase and decreases intracellular pH, acidifies and then suppresses P-gp expression and activity, contributing to the reversal of MDR. In another study, GS was demonstrated to suppress P-gp expression through the COX-2-dependent mechanism, reducing protein levels of COX-2, P-gp, and prostaglandin E2 (PGE2) and reinstating imatinib resistance in K562 cells using Western blot and ELISA [43, 47]. As a pro-drug, the combination of doxorubicin (1 μmol·L^{-1}) and GS (25–100 μmol·L^{-1})) demonstrated a noticeable drop in PGE2 levels and increased doxorubicin cytotoxicity in PLC/PRF/5R liver cancer cells. This finding substantiates that GS augments chemosensitivity through the COX-2/P-gp pathway, rendering it useful as a chemotherapy adjuvant. Moreover, GS controls MDR1 expression at the blood-brain barrier through the PXR-dependent pathway, enhancing drug delivery to the brain [48]. The application of 30 μmol·L^{-1} *Z*-GS to human brain-derived microvascular endothelial cells (hBDMECs) decreases the SRC-1 coactivator expression, thereby inhibiting PXR-mediated *MDR1* gene expression.

In conclusion, GS is a potential approach to the reversal of MDR in cancer treatment. Nevertheless, the available evidence is confined to *in vitro* models and needs to be confirmed *in vivo*. To optimize the clinical potential of MDR reversal and GS, future studies need to clarify the precise mechanisms of MDR reversal and interactions between GS and other chemotherapeutics.

3.2. Anti-inflammatory activities

GS exhibits therapeutic potential in various inflammatory conditions by targeting key signaling pathways, such as NF-κB, ERK, JNK, and STAT3, thereby suppressing pro-inflammatory mediators. For instance, it shows efficacy in IBD (inflammatory bowel disease). In trinitrobenzene sulfonic acid (TNBS)- and oxazolone-induced colitis, 30 mg·kg^{-1}·d^{-1} *E*-GS/*Z*-GS administration (5 days) significantly inhibited colonic expression of TNBS-mediated inflammatory and immune mediators, such as interferon (IFN)-γ, IL-2, IL-6, TNF-α, and TGF-β. This was mediated through the inhibition of IκBα phosphorylation and degradation, which blocked NF-κB binding to DNA and pathway activation [49]. Likewise, GS prevents the dextran sodium sulfate (DSS)-induced acute colitis by inhibiting the NF-κB pathway, which is a typical downstream effector of IL-1β and lipopolysaccharide (LPS). Its protective role in colitis is also connected to triggering receptor expressed on myeloid cells-1 (TREM-1) suppression and macrophage control. GS suppresses NF-κB, AP-1 and proteasome pathways to reduce TREM-1-mediated intestinal inflammation *in vivo* and *in vitro*. GS suppresses TREM-1 expression and augments IL-10 production in TNBS-induced colitis models, increasing the survival of wild-type mice [50]. Moreover, GS reduces the acute pancreatitis induced by cerulein by inhibiting the ERK and JNK activation after intraperitoneal injection [51]. Resveratrol combined with GS inhibits NF-κB and STAT3 activation and decreases TNF-α, IL-1β, and IL-6 expressions in pancreatitis models [52]. These results highlight the potential of GS as a therapeutic agent in inflammatory diseases, which should be studied further.

GS has been widely employed as an anti-inflammatory agent and has a better profile than traditional corticosteroids [53]. Nevertheless, the existing information regarding its anti-inflammatory effect is mainly based on animal and cellular research (Table S2). Additional clinical research is essential to validate its efficacy in human inflammatory conditions.

3.3. Antioxidant stress

GS alleviates oxidative stress through the activation of MAPKs, PI3K/Akt, or Nrf2/heme oxygenase-1 (HO-1) signaling pathways. It is a strong antioxidant that prevents apoptosis and suppresses the pathogenesis of diseases related to the accumulation of reactive oxygen species (ROS), such as diabetes, atherosclerosis, and cancer [54-56]. GS increases cytoprotective enzyme HO-1 in human breast epithelial cells (MCF-10A), with *cis*-GS having higher antioxidant potential than *trans*-GS [57]. Immunocytochemistry and luciferase reporter assays confirmed that *cis*-GS enhances Nrf2 nuclear translocation and binding to ARE (antioxidant response element), leading to HO-1 upregulation. This indicates that GS modulates Nrf2, a key protective factor, *via* activation of MAPKs and PI3K/Akt, providing cellular protection. Another study showed that in glucocorticoid-induced osteoporotic rats, GS alleviates oxidative stress by enhancing antioxidant enzyme activity, increasing GSH (glutathione) levels, and SOD (superoxide dismutase) activity [58]. Its mechanism of action is related to the activation of the Nrf2/HO-1 pathway and the decrease of endogenous oxidative damage, which implies the possibility of its use in osteoporosis treatment.

Moreover, GS is an effective mitigating agent against the destructive effects of oxidative stress on crucial organs, including the heart and brain. It suppresses stroke symptoms due to cerebral thrombosis and the related ROS signaling. In middle cerebral artery occlusion (MCAO) rats subjected to 50 mg·kg^{-1} *Z*-GS treatment, the levels of MDA in blood were reduced, whereas the activities of blood glutathione peroxidase (GSH-Px), catalase (CAT), and SOD were enhanced. The cardioprotective effects of GS were also observed in cases of ischemia [59]. GS infusion did decrease the phospholipase and xanthine oxidase activities and lipid peroxidation and increased the SOD levels, thereby improving the removal of ROS and reducing the level of oxidative stress in isoproterenol-treated rats [60]. Recent reports indicate that GS enhances HO-1 by enhancing ROS-dependent GSK3b (Ser9/21) and p38 phosphorylation and regulating translocation of Nrf2 nucleus, thereby reducing LPS-induced pyogenic liver injury [61]. However, additional clinical research should be conducted to support the antioxidant effects of GS.

3.4. Lipid-lowering effects

GS helps to promote fat breakdown by inhibiting adipocyte-specific TCFs and mitochondrial pathways, thus preventing adipocyte proliferation, differentiation, and excessive energy storage. Early studies showed that oral administration of guggul resin containing GS directly affects adipocytes [62]. Subsequent research confirmed its anti-obesity effects and demonstrated its

ability to reverse FXR activation in 3T3-L1 preadipocytes [63, 64]. Both GS isomers target the adipocytes in a different manner, with *cis*-GS being more effective than *trans*-GS in its ability to induce apoptosis and the degradation of mature adipocytes. The mechanism of action of 3T3-L1 cells is concentration-dependent [65]. GS suppresses preadipocyte differentiation and induces dedifferentiation by downregulating adipocyte-specific TCFs at low concentrations (6.25–50 μmol·L^{-1}), namely, PPAR-γ2, CCAAT enhancer binding protein α (C/EBPα), and C/EBPβ. At elevated concentrations (25–200 μmol·L^{-1}), GS triggers apoptosis by releasing cytochrome c *via* the mitochondrial pathway and by activating caspase-3/7. Recent results indicate that GS enhances mitochondrial density and oxygen uptake in adipocytes and enhances brown adipocyte transcripts (UCP1, TBX1, *β*-3AR) [66]. GS also promotes the anti-obesity effects when used in combination with some drugs, including dyewood extract + GS, hydroquinone + GS, or GS + 1,25(OH)$_2$D$_3$ [67-69].

Moreover, GS prevents obesity-related diseases like atherosclerosis and type 2 diabetes. LDL oxidation is also a cause of atherosclerosis; however, GS inhibits copper ion-, AAPH-, and soybean lipoxygenase-mediated LDL oxidation, retarding the development of foam cells and the disease progression [70]. GS also aids in managing type 2 diabetes. In high-fat diet-fed rats, GS significantly increased PPAR-γ expression and activity. *In vitro*, it reduced harmful lipids—total cholesterol, LDL, VLDL cholesterol, and triglycerides—while elevating HDL levels [71]. By promoting 3T3-L1 preadipocyte differentiation, GS shows promise for developing novel therapeutics for type 2 diabetes.

3.5. Antiviral mechanisms

The antiviral mechanism of GS primarily involves upregulating HO-1 expression to induce interferon responses and inhibit DENV (dengue virus) replication. Initially, GS showed IC$_{50}$ and SI values of approximately 20 μg·mL^{-1} against enveloped viruses (HSV-2 and RSV-B), with antiviral potency increasing with longer virus contact time [72]. In DENV-infected Huh-7 cells treated with 20 μmol·L^{-1} *E*-GS for three days, MTS assays showed dose-dependent inhibition of viral replication without cytotoxicity. Western blot and qRT-PCR confirmed reduced DENV protein and RNA levels, with an EC$_{50}$ of 8.7 ± 1.5 μmol·L^{-1}. *In vivo* validation in 6-day-old ICR mice injected with infectious or heat-inactivated DENV showed reduced brain viral load and downregulated HO-1 and IFN-α-related genes (*IFN-α2*, *IFN-α5*, and *IFN-α17*). The antiviral mechanism involves NRF2-mediated HO-1 upregulation, which inhibits DENV replication by enhancing IFN-related gene expression and downstream antiviral responses *via* DENV NS2B-NS3 protease targeting [73]. Molecular docking and dynamics simulations suggest GS binds stably to SARS-CoV-2 Mpro, proposing it as a lead candidate for COVID-19 therapeutics targeting the viral main protease [74]. Further studies confirm that *Z*-GS regulates ACE2 (angiotensin-converting enzyme 2) *via* FXR, reducing susceptibility of gallbladder, airway, and intestinal cells to SARS-CoV-2 infection *in vitro* [75].

3.6. Neuroprotection

GS possesses neuroprotective properties, including inhibition of neuroinflammatory factors, reversal of neuronal damage, and promotion of neural function recovery. Thus, GS holds promise for treating cerebral ischemia, AD, autism spectrum disorder, MS (multiple sclerosis), depression, and other neurodegenerative diseases.

It has been established that GS has neuroprotective effects in neuropathology through its ability to regulate inflammatory mediators. *Z*-GS showed pronounced anti-inflammatory effects in a neuroinflammation mouse model by suppressing the IκBα–NF-κB signaling pathway, which led to the reduced expression of pro-inflammatory cytokines, such as iNOS, TNF-α, and IL-6 in LPS-activated microglial cells [4]. This suppression attenuated microglial activation and ameliorated neuroinflammation-induced behavioral abnormalities. Later, in research assessing the therapeutic use of GS in ischemic stroke, *Z*-GS was intraperitoneally administered to rat models of MCAO and oxygen-glucose deprivation (OGD). In comparison to low-dose (30 mg·kg^{-1}), high-dose (60 mg·kg^{-1}) treatment treatment proved to be more effective in enhancing neurological recovery and decreasing the volume of infarction after staining brain tissue sections with 2,3,5-triphenyltetrazolium chloride (TTC). Besides, *Z*-GS enhanced post-ischemic histopathological alterations, such as disordered neuronal structure, neuronal death, and nuclear shrinkage. *Z*-GS also significantly lowered the concentration of GFAP, an astrocyte activation protein following a stroke, decreased the mRNA expression of pro-inflammatory cytokines *TNF-α*, *IL-1β*, *IL-6*, *IFN-γ*, and monocyte chemotactic protein-1 (MCP-1), and increased the expression of anti-inflammatory cytokines IL-10 and TGF-β1, which led to a functional recovery and exerted a neuroprotective effect [76]. The neuroprotective impact of *Z*-GS can also be extended to the formation of glial scar after a stroke because there is a beneficial influence on the expression of *Spp1*, which is a vital gene in stroke-induced ischemia-reperfusion injury [77]. These effects were gained at the molecular level, at which *Z*-GS blocked the phosphorylation of JNK and inhibited the activation of the TLR4-mediated pathways. Moreover, GS reduces AD pathology by inhibiting TLR4NF-κB signaling cascade and JNK phosphorylation and reducing the neuroinflammation and synaptic loss of APPswe/PS1dE9 mice. In *Z*-GS-treated APPswe/PS1dE9 mice, *β*-secretase 1 (BACE1) expression was lower, leading to a reduction in amyloid precursor protein (APP) processing and reduction of amyloid-beta (Aβ) and plaque burden in the brain [78]. Additionally, recent evidence indicates that GS selectively inhibits astrocyte activation and vesicular release of pro-inflammatory cytokines within the dorsal horn of the spinal cord, which offers a treatment alternative to pain in neuropathy. GS, when used intraperitoneally, decreased mechanical and thermal hypersensitivity in chronic constriction injury (CCI) mice. The immunofluorescence and ELISA analysis confirmed that GS suppressed the expression of GFAP and reduced IL-1β, IL-6, and TNF-α concentrations in the spinal dorsal horn of CCI mice, which validates its analgesic effect [79].

GS has also shown therapeutic efficacy in autism spectrum disorders (ASD) and MS in the central nervous system through the regulation of JAK-STAT signaling pathway. Oral GS administration at 60 mg·kg^{-1} over a 43-day period in a rat model of autism induced by ICV-PPA injection considerably enhanced motor behavior, neuromuscular coordination, spatial memory, cognition, and weight gain [80]. Prolonged therapy decreased STAT3 protein levels in the brain homogenates and cerebrospinal fluid during ELISA measurements and elevated the expressions of PPAR-g and MBP (myelin basic protein). Moreover, GS rescued dopamine and acetylcholine losses and prior elevations of glutamate. In addition, GS inhibited the development of MS by inhibiting the upregulation of JAK/STAT and reversing downregulation of PPAR-γ [81]. MBP is an important indicator of myelin integrity, and demyelination is a feature of MS [82]. GS treatment (60 mg·kg^{-1}) elevated MBP levels in rats that were demyelinated with ethidium bromide, implying that it is involved in the prevention of demyelination and enhancement of remyelination. These findings indicate that long-term GS therapy exerts neuroprotective action on GS-induced models of MS. It was also reported recently that oral GS (30 and 60 mg·kg^{-1}) administration is observed to influence the effects of MeHg^{+} on STAT-3, mammalian target of rapamycin (mTOR), and PPAR-γ in adult Wistar rats. This modulation demonstrates markedly reduced behavioral, motor, and cognitive performance, improved myelin regeneration, and diminished neuroinflammation, which suggests its future application in the treatment of amyotrophic lateral sclerosis (ALS) [83].

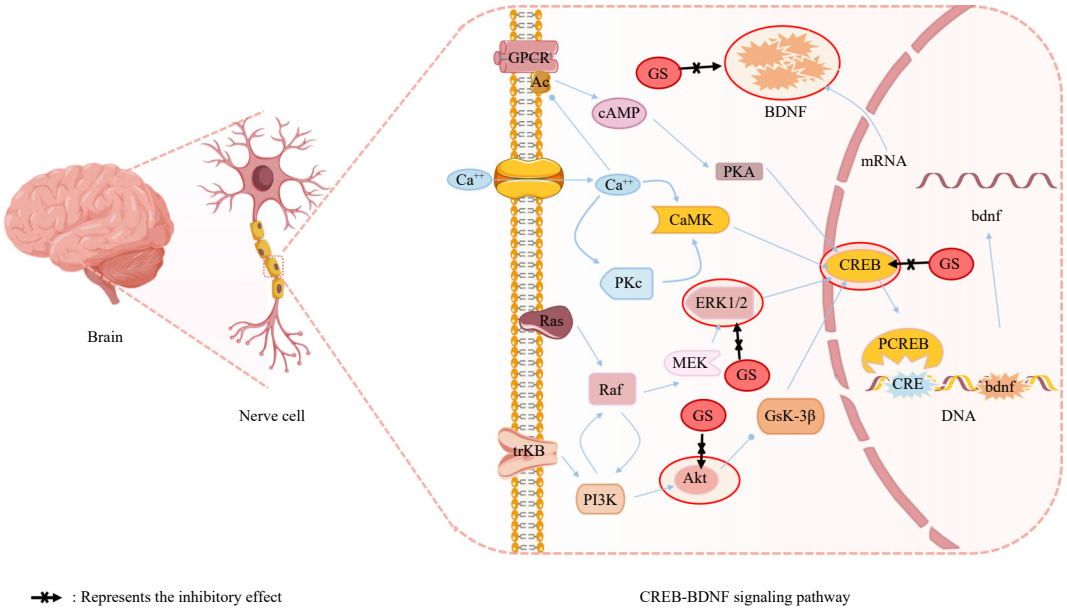

Fig. 3 GS activates the CREB-BDNF signaling pathway to play a neuroprotective role.

Despite the paucity of research studies on the neuroprotective property of GS, early evidence indicates that it safeguards the nervous system by engaging with the CREB/BDNF signaling pathway (Fig. 3). Re-treatment of mice with GS (30 or 60 mg·kg^{-1}) was effective in reversing memory impairment caused by scopolamine. This reversal was linked to recovered phosphorylation of CREB, ERK1/2, and Akt in the hippocampus and cortex, and elevated BDNF protein expression [84]. *Z*-GS, like fluoxetine, is protective against major depressive disorders. In mouse behavioral studies, such as the tail suspension test (TST) and forced swim test (FST), 10 and 30 mg·kg^{-1} doses significantly reduced immobility time, reversed anhedonia, as indicated by the amount of sucrose intake, and improved neurogenesis, as indicated by an increased number of cells with doublecortin (DCX)-positive or up-regulated expression of neurogenic proteins [85]. These findings show that *Z*-GS can significantly inhibit neurodegeneration of the hippocampal caused by copper sulfate ($CuSO_4$), activate the BDNF signaling pathway, and induce antidepressant-like effects.

3.7. Cardioprotection

GS has a strong protective influence on the cardiovascular system. It reverses myocardial necrosis induced by isoproterenol, replenishes cardiac myocardial abundances of creatine kinase, phospholipase, cardiac glycogen, and phospholipids, and prevents degradation of cytochrome P450, b5, and hemoglobin in injured cardiomyocyte [86]. Further research also demonstrated that GS isomers prevent the peroxidation of low-density lipoprotein by metal ions and the formation of superoxide anions (O^{2-}) and hydroxyl radicals (OH), thus providing cardioprotection [87]. GS also safeguards myocardial tissue through the inhibition of mitochondrial-mediated apoptosis and endoplasmic reticulum stress. The GS treatment in cholesterol-fed mice was observed to significantly decrease the myocardial infarct size, cardiomyocyte apoptosis index, caspase-12 activities, CHOP and Bax/Bcl-2 ratio [88]. Moreover, GS prevents myocardial injury caused by doxorubicin. Immunoblotting showed that GS treatment augmented expressions of PARP, caspase-3, and Bcl-2 in H9C2 cells while reducing Bax, cytochrome C release, cleaved-PARP, and cleaved-caspase-3 [89]. GS lowers intracellular production of ROS and MDA through its antioxidant activity, which suppresses cardiac toxicity caused by DOX. Despite the proven cardioprotective effect, the exact mechanism of action of GS has not been fully elucidated yet and needs additional research in the laboratory.

3.8. Antifibrosis

GS has a high potential to be used as a therapeutic agent in chronic kidney disease and liver fibrosis because of its high antifibrotic activity. GS has been indicated to play a critical role of decreasing the rate of renal fibrosis in chronic kidney disease and in preserving normal renal function. GS has been noted to greatly lessen renal injuries in a mouse of unilateral ureteral obstruction-induced kidney fibrosis by inhibiting the expressions of alpha-smooth muscle actin (*α*-SMA), TGF-β, and collagen, thus preventing fibrogenesis [90]. Moreover, *in vitro* experiments revealed that GS increases the survival of hypoxia-exposed HK-2 cells, which delays fibrotic alteration caused by hypoxia. Likewise, GS exerts antifibrotic effects on liver fibrosis, in which hepatic stellate cells are pivotal in the pathogenesis of the disease. In an LX-2 cell model, GS inhibits collagen α1 transcription and disturbs intracellular *α*-SMA expression, effectively stopping fibrotic progression [91]. In addition, GS induces apoptosis of hepatic stellate cells and prevents the activation of NF-*κ*B, which suppress liver fibrosis. All these observations support GS as a prospective dietary supplement to the organ-wide antifibrotic regimen. However, further research is necessary to fully explain its mechanism.

4. Pharmacokinetic study of GS

Systemic efficacy of drugs is affected by a number of factors such as solubility, gastrointestinal stability, gastric emptying, intestinal transit time, intestinal and hepatic permeability, and first-pass metabolism [92]. Extensive research has been conducted on the pharmacokinetics of GS. In the late 20th century, rat studies evaluated GS pharmacokinetics following oral and intravenous administration at doses of 30 and 10 mg·kg^{-1}, respectively [93]. Nevertheless, the results of these initial studies were inconclusive because the sensitive and selective bioanalytical techniques are limited. Subsequently, it was found that there were species-specific differences in GS metabolism between SD rats and NZ rabbits [94]. Building on this, the ADME (absorption, distribution, metabolism, and excretion) profiles of *E*- and *Z*-GS were clarified using LC-MS/MS technology in both *in vitro* and *in vivo* settings. The data revealed rapid oral absorption, with a mean c_{max} (peak plasma concentration) of 59.37 ± 2.32 ng·mL^{-1} for *E*-GS and 108.20 ± 28.53 ng·mL^{-1} for *Z*-GS. Both isomers exhibited extensive distribution into extracellular tissues, with $V_{d/F}$ values of

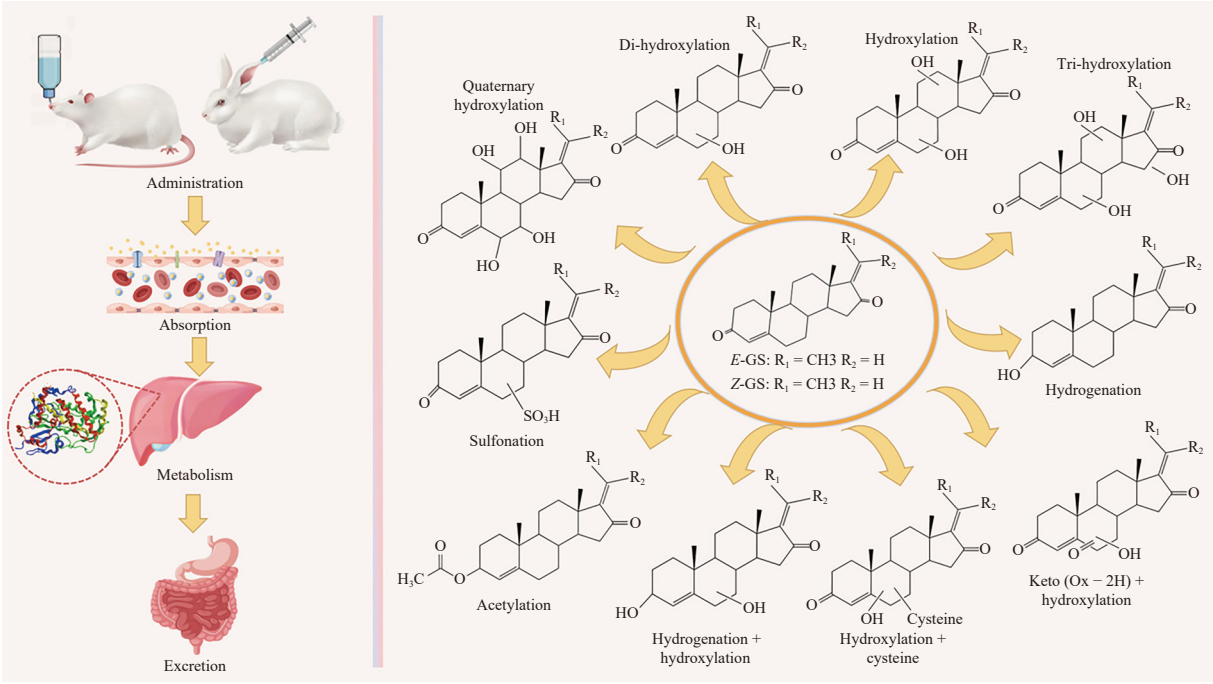

Fig. 4 Metabolic processes and the putative metabolites of GS.

186.39 ± 39.95 L·kg^{-1} (*E*-GS) and 151.52 ± 76.78 L·kg^{-1} (*Z*-GS). They also displayed high plasma protein binding and stability in simulated gastric and intestinal fluids. Absolute oral bioavailability (F%) after hepatic metabolism was low—1.26% ± 0.89% for *E*-GS and 2.10% ± 0.48% for *Z*-GS [95]. Furthermore, both isomers showed high clearance rates relative to hepatic plasma flow, at 2.79 ± 0.73 and 3.01 ± 0.61 L·h^{-1}·kg^{-1}, respectively, and short elimination half-lives of 0.63 ± 0.25 and 0.74 ± 0.35 h. GS primarily undergoes oxidative metabolism mediated by P450 enzymes in hepatic mitochondria (Fig. 4). Using human hepatic mitochondria and S9 fractions, researchers identified 19 phase I and phase II metabolites, with hydroxylation being the predominant metabolic pathway [96].

In conclusion, *E*-GS and *Z*-GS exhibit wide distribution in extracellular tissues in rats, high plasma protein binding, but rapid degradation following oral administration. They display high clearance rates and short half-lives, resulting in low systemic bioavailability.

5. Toxicity of GS

GS is recognized for its pharmacological properties and is generally considered to have a favorable safety profile compared to many conventional drugs. Most drug toxicities arise from RMs (reactive metabolites) and their interactions with cellular proteins. RMs were characterized, and ADMET Predictor™ software was used to predict the potential toxicity of GS and its metabolites [97]. Results indicated that GS-containing formulations may cause adverse reactions such as erythema, papules, rashes, facial swelling, itching, headache, and hepatotoxicity [98]. It was reported that there were no significant adverse effects on the renal or liver functioning, hematological parameters, and electrolytes in people who were given oral GS over a period of six months [99, 100]. A preclinical toxicological study was recently carried out in Sprague-Dawley rats with a Ayurvedic formulation, BPGrit, which comprised of *E*-GS and *Z*-GS. Repeated oral dosing of 100, 300, and 1000 mg·kg^{-1}·d^{-1} did not lead to mortality, morbidity or abnormal clinical events. There was no evidence of any alteration of blood parameters, biochemical indicators, or histopathology even at the highest dose (1000 mg·kg^{-1}·d^{-1}) [101].

Together, the literature indicates that GS is relatively less toxic at the recommended dose levels, which means that the compound can be used as a safe drug candidate in the development of future drugs. However, toxicity profiles needs extensive *in vitro* and *in vivo* studies to confirm its safety profile and facilitate its future clinical translation.

6. Derivatives of GS

Although GS has a promising pharmacological activity, it could cause severe adverse reactions in the case of oral or rectal intake. In order to improve safety and maintain therapeutic effectiveness, researchers have produced and tested a number of derivatives (Fig. 5). To improve the inhibition of NF-κB signaling in intestinal epithelial cells and overcome colitis caused by DSS, a series of new poorly soluble lipophilic GS derivatives were developed using an enhanced framework [102]. Among them, GS-52 exhibited the most potent anti-inflammatory activity at 100 mg·kg^{-1} hen administered rectally. It alleviated the loss of body weight, shortening of the colon, and disease activity index (DAI), inhibited the NF-κB signaling in TNF-α-stimulated COLO 205 cells, and increased IL-8 expression. It is important to note that

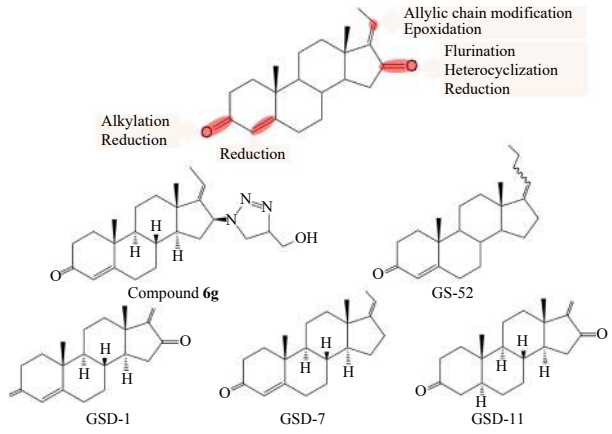

Fig. 5 Modified sites of GS and its derivatives.

GS-52 was equally as effective as sulfasalazine or prednisolone when used in models of colitis. It potently inhibited the expressions of *IL-12p40* and *TNF-α* in BMDCs stimulated by LPS, facilitated IκBα degradation, and reduced NF-κB DNA binding activity, which possesses therapeutic value in IBD [103]. Moreover, GS-52 demonstrates the promise of being a gastric mucosal protective agent that activates MAPK, IKK, and IL-8 expressions in gastric epithelial cells, suppresses NF-κB signaling, and mitigates ethanol-induced gastric injury in mice [91]. In another study on nephroprotection, *E*-GS demonstrated nephroprotective activity with modest potency at 125 μmol·L^{-1}. GS derivative (**6g**), prepared through [3 + 2] click chemistry using aryl and alkyl acetylenes [104], exhibited better cytoprotection. When added at 25 μmol·L^{-1} to cisplatin-injured renal cells, it produced an increased cell survival in comparison to NAC (*N*-acetylcysteine). It protected against cisplatin-induced nephrotoxicity by significantly reducing phosphorylated JNK, p38, and cleaved caspase-3 levels *via* inhibition of the MAPK pathway. GS derivatives have also become a new category of anticancer agents, which is known as "antishrinkage agents", because it is selective and effective in treating cancer [105, 106]. GSD (GS derivative)-7, GSD-1, and GSD-11 showed concentration-dependent cytotoxicity in the nutrient-deprived PANC-1 tumor cell line, with PC_{50} values of 1.6, 3.2, and 0.72 μmol·L^{-1}, respectively. The compounds suppressed cell migration, triggered cell shrinkage, swelling, and cytoplasmic leakage, and eventually led to cell death after 12 h. Western blot analyses revealed that they inhibited the Akt/mTOR pathway to suppress the survival of PANC-1 cells. Remarkably, GSD-1 inhibited IκBα degradation and p65 phosphorylation to prevent p65 nuclear translocation and further activation of upstream kinases (TAK1, IκBα, and IκBβ) [106]. The results herein indicate the direct anticancer and antimetastatic effect of GSDs in human breast cancer cells.

In conclusion, GSDs display improved drug pharmacological activity, therapeutic effect, and safety profiles. Further research and development will broaden their clinical uses and provide new therapies to different diseases.

7. Discussion and future perspective

Future studies should consider a number of areas to speed up the development and use of GS-related therapeutics.

High-level extraction, separation, and synthesis methodologies are needed to enhance the quality of GS and sustainable production. Nowadays, GS isolation is afflicted by co-extraction with terpenoids, sterols, and flavonoids. These impurities are usually not entirely removed by the conventional purification techniques, compromising the purity and usability of products. Supercritical fluid extraction and membrane-based separation based on the molecular characteristics are advanced techniques to obtain high-purity GS, allowing for effective enrichment and purification. Moreover, conventional synthetic methods have disadvantages, such as the use of toxic reagents, lack of selectivity and low yields. Advanced strategies are still underdeveloped. Thus, further attempts should be made to optimize the current approaches to achieve shorter, safer, greener, and more affordable synthetic routes.

The correlation between structure and activity should be clarified so as to utilize the therapeutic potential of GS in a range of pathologies. Despite the fact that most recent studies have focused on animal and cellular cancer models, there are few and robust clinical findings of GS efficacy in deterring or treating disease, which hampers mechanistic research. In the future, combining crystallography, molecular docking simulation, and biophysical assays to ascertain the effects of structural changes on target engagement should also be carried out, and this will aid in understanding the presence of unmistakable links between structure, target, and biological activity. The artificial intelligence algorithms can be applied to the vast amounts of GS structures and their associated efficacy to forecast the outcome of chemical modifications. Computational methods like MD simulations are able to simulate GS behavior *in vivo* to direct rational optimization of structures. This integrative strategy will accelerate the process of structure-efficacy research and will provide a excellent theoretical foundation to create more efficient and safe GS-based drugs. Moreover, additional studies are required to determine how the GS structure can be adapted to different cellular and tissue environments to elicit the best therapeutic outcome, including optimization of structure to fit the metabolic environment and target delivery of tumor tissues to increase anticancer responses.

The expansion of the clinical application of GS is based on the formulations with high bioavailability and targeted delivery. The existing constraints include fast oral bioavailability and clearance, and these factors impair the therapeutic efficacy. The introduction of some chemical functional groups into the GS molecule would alter its physicochemical characteristics, such as its solubility, stability, and membrane permeability, which may result in improved gastrointestinal absorption and reduced metabolic degradation, thereby improving bioavailability. For example, the hydrophobic group can be added to increase lipophilicity and absorption efficiency. Another strategy to enhance therapeutic responses and minimize off-target effects and adverse reactions of GS is to encapsulate GS with non-toxic, biodegradable and target-specific nanocarriers such as PLGA, chitosan, silk fibroin, or liposomes.

8. Conclusion

GS is a natural compound mostly derived from plants of the *Commiphora* and *Boswellia* genera. It exhibits wide-ranging pharmacological activities through modulation of various signaling pathways, such as JAK/STAT3 and Nrf2/HO-1. Although GS is not orally bioactive, it is highly metabolized in the liver and is less toxic at low doses, which means it can be applied in the clinical development. To achieve the full therapeutic potential of the structure, future studies need to focus on structural modification, the mechanistic clarification, and novel formulation design.

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Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

The authors declare no competing financial interest.

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