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Revisiting liquorice (*Glycyrrhiza glabra* L.) as anti-inflammatory, antivirals and immunomodulators: Potential pharmacological applications with mechanistic insight.

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**ABSTRACT**

**Background:** *Glycyrrhiza glabra* (G. glabra) commonly known as liquorice is one of the highly exploited and utilized medicinal plant of the world. Since ancient times liquorice is considered as an auspicious and valuable traditional medicine across the world for treatment of various ailments.

**Method:** Several electronic online scientific databases such as Science Direct, PubMed, Scopus, Scifinder, Google Scholar, online books and reports were assessed for collecting information. All the collected information was classified into different sections to meet the objective of the paper.

**Results:** The electronic database search yielded 3908 articles from different countries. Out of them one ninety-eight articles published between 1956 and 2021 were included, corresponding to all detailed review on *G. glabra* and research on anti-inflammatories, antivirals and immunomodulatory through pre-clinical and clinical models. From all selective area of studies on *G. glabra* and its bioactive components it was established (including molecular mechanisms) as a suitable remedy as per the current requirement of pandemic situation arise through respiratory tract infection.

**Conclusion:** Different relevant studies have been thoroughly reviewed to gain an insight on utility of liquorice and its bioactive constituents for anti-inflammatories, antivirals and immunomodulatory effects with special emphasized for prevention and treatment of COVID-19 infection with possible mechanism of action at molecular level. Proposed directions for future research are also outlined to encourage researchers to find out various mechanistic targets and useful value added products of liquorice in future investigations.

**List of Abbreviation**

- AIM (Absent in melanoma);
- ASC (Apoptosis-associated speck-like protein cell);
- BMDMs (Bone marrow-derived macrophages);
- BMI (Body mass index);
- CD4+ (Cluster of differentiation);
- COX (Cyclooxygenase);
- CPE (Cytotoxic effect);
- CXCL (Chemokine (C-X-C motif) ligand 2);
- DHV (Duck Hepatitis Virus);
- ERK1/2 (Extracellular signal-regulated kinases);
- Fox O (Forkhead box O);
- H1N1 (Hemagglutinin Type 1 and Neuraminidase Type 1);
- HIF-1 (Hypoxia-inducible factor);
- 10-HDoHE (Hydroxydocosahexaenoic acid);
- 5-HETE (5-Hydroxyeicosatetraenoic acid);
- HMGP B1 (High mobility group protein B1);
- ICAM-1 (Intercellular adhesion molecule-1);
- IFN-\(\gamma\) (Interferon-gamma);
- SCI (Science Information Co-ordination)
- SCOPUS (Source Normalized Impact Factor)
- ESI (Editors' Selection)
- SCIFINDER (Science Citation Index Expanded)
- Elsevier (ScienceDirect)

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IL (Interleukin); iNOS (Inducible nitric oxide synthase); IgE (Immunoglobulin E); JNK (c-Jun N-terminal kinases); LOX (Lysyl oxidase); LPS (Lipoplysaccharide); LTB4 (Leukotriene B4); MAPK (Mitogen-activated protein kinase); MDC (Monocyte-derived chemokine); MHC (Major histocompatibility complex);

Mpro (Main protease); mRNA (Messenger RNA); NF-kB (Nuclear factor kappa-light-chain-enhancer of activated B cells); NLR (Nucleotide-binding domain leucine-rich repeat); NO (Nitric oxide); NOD (Nucleotide-binding oligomerization domain-like receptors); OVA (Ovalbumin); PBMC (Peripheral blood mononuclear cell); PDEP5 (Phosphodiesterase-5);

Fig. 1. Chemical structure of phytochemicals present in G. glabra L.
Introduction

Glycyrrhiza glabra L. (Fabaceae) (common name liquorice) is a valuable medicinal plant. Its name derives from the Greek words ‘glykos’ that means sweet and ‘rhiza’ that means root (Sharma et al., 2018). The genus Glycyrrhiza comprises more than 30 species that are extensively dispersed worldwide mainly at Mediterranean regions of Asia (Sharifi-Rad et al., 2021). This plant has been documented and reviewed as a traditional remedy for the prevention of painful swellings, cough, colds, and influenza. (Pastorino et al., 2018; Hosseini et al., 2020; Nasiri et al., 2020). G. glabra and its bioactive phytochemicals holds multiple pharmacological activities like, antidemulcent, expectorant, antiulcer, anti-inflammatory, anticancer and anti diabetic as an evidence from many published studies (Fig. 1) as drug of choice to explore it more precisely for multiple health benefit possibilities as an evidence from many published studies reviewed in past (Revers, 1956; Ren and Wang, 1988; Olukoga and Donaldson, 2000; Saxena, 2005; Asl and Hosseinzadeh, 2008; Kaur et al., 2013; Kao et al., 2014; Hosseinzadeh and Nasiri-Asl, 2015; Yang et al., 2015; Dastagir and Rizvi, 2016; Pastorino et al., 2018; Sharma et al., 2018; Bredin, 2019; Mamedov and Egamberdieva, 2019; Battha et al., 2020; Chen et al., 2020a; Jiang et al., 2020; Kwon et al., 2020; Rehman et al., 2020; Wang et al., 2020; Hasan et al., 2021; Sharifi-Rad et al., 2021). Further, utility through novel drug delivery specially nanomedicine approaches, cosmeceutical application and as an animal feed alternative are well discussed and reviewed recently (Alagawany et al., 2019; Ciganovic et al., 2019; Rani et al., 2021). The current piece of this illustrative work will provide motivation on growing interest in coming years about concept of drug repurposing for a better understanding of the indication based drug discovery strategies for the treatment of many related clinical and pathological conditions and thus may direct future research.

In nutshell, the present review documented recent scientific evidence available on pharmacology focussing antiinflammatory, antivirals and immunomodulatory effect with special emphasized for the prevention and treatment of COVID-19 infection by involvement of molecular mechanism to direct future research for bringing liquorice to develop several value added products for commercialization.

Materials and methods

The exhaustive search of literature was accomplished with the information retrieved by using online electronic search engines/data bases/publishers and websites such ACS, Google Scholar, PubMed, Science Direct, Taylor and Francis, Wiley etc., using G. glabra as the searching keyword. Publications not falls in criteria and non-Scopus indexed journals were excluded from the study. All the composed information retrieved through online literature search is further classified into different sections according to the requirement and objective of the paper.

Production and Metabolism

In a one of past study highest glycyrrhizin (2.5 mg/g dry weight) content through transgenic roots culture was obtained, which was approximately, 2.6 times higher than control hairy roots culture (Lu et al., 2008). In a study, CYP88D6, a cytochrome P450 monooxygenase gene was identified as a glycyrrhizin-biosynthetic gene, through transcript profiling-based selection from a collection of liquorice expressed sequence tags (Seki et al., 2008). It was further confirmed through an in vitro study on 65-day-old cultured plants. It was found that both salicylic acid and methyl jasmonate are responsible for production of glycyrrhizin and plant growth (Shabani et al., 2009). Similarly, in another study methyl jasmonate (100 µM) was found to be responsible as most efficient elicitors for the production of glycyrrhizin (109 µg/g dry weight on day 5 of elicitation) (Wongwicha et al., 2011). It was further reveal through another study that CYP72A subfamily proteins was act as a
genetic tool for production of glycyrrhizin through genetic engineering (Seki et al., 2011). In this connection use of elicitors in the production of glycyrrhizin for enhanced production of glycyrrhizin up to 108.9 ± 1.15 µg/g was further verified through another study (Putalun et al., 2011). Production of glycyrrhizin up to 8.6-fold through the application of cellulase based elicitor by using G. glabra root culture was further studied (De Oliveira et al., 2014). In a very recent study on G. glabra an improved formation of glycyrrhizin to a quick extent over a year and without changing in plant composition was observed. Where, A4 strain of Agrobacterium rhizogenes help to generate hairy root cultures of G. glabra. The amount of glycyrrhizin has been elevated by employing various biotic as well as abiotic elicitors such as CdCl$_2$, cellulose, polyethylene glycol (PEG), and mannan-oligosaccharide. Addition of 1% concentration of PEG can cause the glycyrrhizin up to 5.4-fold higher after 24 h of vulnerability, while 200 µg/ml cellulose has elevated the amount of glycyrrhizin up to 8.6-fold after one week of exposure, whereas 10 mg/l concentration of mannan-oligosaccharide has hastened the formation of glycyrrhizin around 7.8-fold after 10 days of stress (Srivastava et al., 2019).

Metabolism

Glycyrrhizin along and other phytoconstituents present in liquorice followed various metabolic pathways are discussed and described in Fig. 2 (Zhao et al., 2018; Abdel-Wahab et al., 2021).

Potential health benefit of G. glabra as anti-inflammatory, antiviral and immunomodulatory agents

Several studies claiming antiinflammatory, antiviral and immunomodulatory action of G. glabra, bioactive compounds and its formulation along with possible mechanism of action are included and presented in table 1, 2 and 3. Some of the highlighted studies are mentioned below as per progressive development on individual section.

Anti-inflammatory activity

An earlier study concluded that both glycyrrheticin acid and aqueous extract of liquorice possess anti-inflammatory activity, which was comparable with diclofenac sodium. Additionally, it was further recommended that activity of anti-inflammatory formulations such as famotidine or diclofinac can be further enhanced through addition of liquorice aqueous extract (Aly et al., 2005). Subsequently, ethanol extract obtained from liquorice was exhibited to improve in the survival rate, reduced plasma levels of TNF-α and IL-6, and increased IL-10 production in LPS-treated mice (Kim et al., 2006). Further, mechanism of anti-inflammatory action of glycyrrhizin by probably due to without involving ROS and without inhibiting neutrophil functions was postulated (Racková et al., 2007). Similarly, in another study, it was found that liquorice extract was able to inhibit proinflammatory cytokine through inhibition of LPS-induced IL-1β, IL-6, IL-8 and TNF-α responses of macrophages. Additionally, liquorice extract was found to be inhibited the phosphorylation of macrophage responsible for intracellular signaling inflammatory proteins pathways including NF-kB p65 nuclear and Jun proto-oncogene-encoded activator protein (AP)–1 transcription factor (Bodet et al., 2008). In another study glycyrrhizin failed to exhibit inhibitory effect through both COX and LOX. However, G. glabra (without glycyrrhizin) exhibits potent anti-inflammatory through PGE-2, TXB-2 and LTB-4 inhibition as an evidence from mammalian cell assay study. It was further postulated...
that anti-inflammatory action might be due to the presence of glabridin and isoliquiritigenin (Chandrasekaran et al., 2011). Which was further supported by another similar study establishing significant anti-inflammatory activities of extract and phytoconstituents (Nirmala and Selvaraj, 2011). During subsequent study on various extracts of liquorice, ethyl acetate extract was found to have significant anti-inflammatory effects, which was due to the presence of mainly polyphenols, flavonoids and dihydrostilbenes (Siracusa et al., 2011). In search of bioactive anti-inflammatory moiety, it was demonstrated that 5-(1,1-dimethylethyl)-3,4,4′-tri-hydroxy-2-methoxychalcone, licochalcone A and B, echinatin and glycyocumarin have ability to inhibit the NO, IL-6 and PGE2 productions (Fu et al., 2013). Further, dihydristilbenes obtained from liquorice are considered to be preferred ligands for COX-2 instead of COX-1 (Trombetta et al., 2014). Progressively in another study on LPS-treated macrophages incubated with methanol extract of *G. glabra* (100 μg/ml) led to improvement of cell viability from 66.6 to 99%. Further, down regulation of NO and productions of ROS in a dose-dependent manner was established. Additionally, mRNA and protein expressions of iNOS suppression, COX-2, cytokines, TNF-α, IL-1β and IL-6 productions was observed (Li et al., 2015). Similarly, bioactive such as liquoritinin, glycyrrhetinic acid and liquiritigenin was found to inhibit LPS-induced pro-inflammatory mediator elevation including iNOS, COX-2, TNF-α, IL-1β and IL-6 in BV2 cell line. However, liquorice extract was found to inhibit pro-inflammatory cytokines expression such as IL-1β, TNF-α, and IL-6) in t-BHP-treated mice liver (Yu et al., 2015). Progressively, a similar study on liquorice extract and its phytoconstituents established anti-inflammatory activity by involvement of TNF, PGE2, MMPs and free radicals cascade (Yang et al., 2017). Further, protective effect on gastric tumorigenesis by 18-β-glycyrrhetinic acid was established by anti-inflammatory activity through PGE2-EP2 receptor-mediated arachidonic acid pathway (Cao et al., 2018). In another study, two isolates namely isoliquiritigenin and naringenin from liquorice was identified to improve T cells synthesis and regulation involve for anti-inflammatory action (Tiwari et al., 2018). In another study both extract and isolated compound licofilavonane was found to exhibit anti-inflammatory action on LPS-induced RAW264.7. It was further revealed that licofilavonane cause downregulation of pro-inflammatory cytokines, expression of COX-2/iNOS levels and modulation of NF-kB/MAPK pathway (Frattarulo et al., 2019). Some liquorice flavonoid including leuckotriene B4, t-acyetyl carnitine, N-linoleoyl taurine, linoleic acid, tryptophanamide, and corticosterone suppress both formaldehyde-induced mice paw edema and alleviated the inflammation through involvement of multiple pathways (Yu et al., 2019). Moreover, multiple mechanism of action by which liquorice can contribute for development of anti-inflammatory responses are studied (Man et al., 2020). Further combination of *Chrysanthemum zawadskii*, peppermint and *Glycyrrhiza glabra* down-regulate anti-inflammatory mediators rise and pro-inflammatory cytokines production induced by LPS (Cho et al., 2021). Among root and leaves, root extract was found to be more cyto-protective by significantly inhibiting the pro-inflammatory cascade (Marotti et al., 2021). In a very recent study the levels of IL-5, GTP, IL-13, GOT (on day 51), mRNA expression of eotaxin, CCL11, CCL24, COX-2, mucus secretion, eosinophil infiltration, and goblet cell hyperplasia was attenuated by the treatment of *G. glabra* was further support the same (Sun et al., 2021). In summary, Glycyrrhetinic acid and glycyrrhizin prohibit tissue inflammation by extenuating ROS formation and have the potency to inhibit IL-3, IL-5, IL-10, IL-12, IL-13, IL-1β, TNF-α, PGE2, MMPs and IL-6 productions was observed (Li et al., 2015). Further combination of anti-inflammatory activity through PGE2-EP2 receptor-mediated arachidonic acid pathway (Cao et al., 2018). In another study, two isolates namely isoliquiritigenin and naringenin from liquorice was identified to improve T cells synthesis and regulation involve for anti-inflammatory action (Tiwari et al., 2018). 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### Antiviral activity

*G. glabra* and its bioactive components is well recognized and reviewed through several authenticated research findings for accompanying antiviral effects against several kinds of viruses such as DNA virus like Herpes Simplex Virus-1, Kaposi sarcoma-associated herpesvirus, Varicella zoster virus, Epstein Barr virus, Human Cytomegalovirus, etc. and RNA viruses such as Influenza A virus (IAV), H1N1 virus, H5N1 virus, Hepatitis C virus, Rotavirus, Newcastle disease virus, Human Immunodeficiency Virus, SARS-associated coronavirus and express its action via blocking the viral replication process (Nasiriasi and Hosseinzadeh, 2007; Baltina et al., 2009; Anagha et al., 2014; Wang et al., 2015; Fukuchi et al., 2016; (Sun et al., 2019) Huaccho-Rojas et al., 2020; Huan et al., 2020; 2021). In an earlier study GD4 (without any glycyrrhizic acid), compound obtained from liquorice was found to be effective antiviral agent against respiratory syncytial virus (RSV) with median TC50 (0.23 mg/ml), EC50 (28.73 μg/ml) and TI (8) (Wang et al., 2006). The major mechanisms for antiviral activity of various species of liquorice was described as reduced membrane transport, hepatitis B virus surface antigen sialylation, membrane fluidity reduction, may inhibit fusion cell with viral membrane of HIV-1, induction of interferon gamma in T-cells, inhibition of phosphorylating enzymes in vesicular stomatitis virus infection and overall reduction of viral latency (Fiore et al., 2009). Progressively another study investigated antiviral effect of glycyrrhizic acid against HCV with 50% reduction at a concentration of 14 ± 2 μg. It was postulated due to inhibition of full length viral particles and core gene expression or function in a dose dependent manner with synergistic effect with interferon (Ashfaq et al., 2011). Moreover, therapeutic glycyrrhizin concentrations (25 to 50 μg/ml) substantially found to inhibit H5N1-induced expression of the pro-inflammatory molecules CXCL10, IL-6, CCL2, and CCL5. The major mechanism behind the activity was interference with H5N1 replication and H5N1-induced

| Plant part/Extract/derivatives | Pharmacological Functions | Mechanism | Doses | Reference |
|-------------------------------|--------------------------|----------|-------|-----------|
| GutGard™ (Standardized root extract of *G. glabra*) | Anti-inflammatory action through COX and LOX inhibition - An *in vitro* studies | Inhibition of LPS induced COX-2 and LOX expression, PGE2, TXB2 and LTB4 productions. | 100 and 1000 μg/ml | Chandrasekaran et al., 2011 |
| Aqueous extract | Rheumatoid arthritis (an anti-inflammatory effect by antigen induced arthritis) | Inhibit serum levels of TNF-α and reduces antigen induce arthritis symptoms in mice. | 300 μg/ml | Abd et al., 2015 |
| Methanol extract | Anti-inflammatory effect (LPS-induced inflammation on RAW macrophages) | Decrease ROS and cell death by suppressing the activity of LPS induced macrophages. Downregulation of mRNA and protein expressions of iNOS, COX-2, cytokines, TNF-α, IL-1β, and IL-6 productions. | 12.5–200 μg/ml | Li et al., 2015 |
| Methanol extract and glycosyl-enriched fraction | Anti-inflammatory Activity | Block viral replication by acting on neuraminidase enzyme. | 1.70 and 0.33 μg/ml | Grieken et al., 2014; Grieken et al., 2013 |
| Liricose flavonoids | Pulmonary inflammation | Reduces the TNFα, IL-1β mRNA expression, elevated lung water content, and pulmonary inflammation by inhibiting the inflammatory cells infiltration and inflammatory mediator release which subsequently reduces neutrophil recruitment. | 3, 10 and 30 mg/kg | Xie et al., 2009 |
| Compounds | Pharmacological Functions | Mechanism | Doses | Reference |
|-----------|---------------------------|-----------|-------|-----------|
| Phytocomplexes of Leaves containing Licoflavanone (13) | Antioxidant and Anti-inflammatory activity (In vitro studies) | Inhibits LPS-induced expression of IL-1β, IL-6 and TNF-α. Decreases iNOS and COX2 expression levels. Interferes with the inflammatory cascade conciliated by NO and PGE2. Prohibits phosphorylation and activation levels of signaling molecule of the MAPK pathway (ERK1/2, JNK, and p38MAPK) and interfere with NK-β MAPK pathways. | 12.5-25 μg/ml | Fratarusso et al., 2019 |
| Phytocomplexes of Leaves (Di(hydro)stilbenes) Poly saccharide fraction obtained from root and shoot | Antioxidant and anti-inflammatory activity (In vitro studies) Immunomodulatory effect | Decrease release of TNFα and PGE2 in whole blood and inhibit only PGE2 release. Produce nitric oxide by murine peritoneal macrophage activity. | 100 μg/assay | Siracusa et al., 2011 |
| | | Induction of IL-1, IL-6 and IL-12 productions, pinocytic activity and stimulates macrophages to produce NO. | 25, 50, 100 and 200 μg/ml | Nose et al., 1998 |
| Purified fraction of water-soluble polysaccharides (10 kDa) | Immune modulatory activity (An in vitro and in vivo studies) | Up-regulation of the relative expression of the IL-7 gene that controls the release of immune cytokine, IL-7 and inhibit the proliferation of tumor cell CT-26. | 50 μg/ml | Ayeka et al., 2016 |
| Polysaccharides | Immune modulatory and anti-cancer activity (CT-26 colon carcinoma cell and cytokine IL-7)- In vitro studies | Suppress tumor growth, increase organ weight, organ index and activate immune cells through activation of secretion of anti-inflammatory cytokines IL-2, IL-6, IL-7. Suppress secretion of pro-inflammatory cytokines and TNF-α. Activate CD4+ and CD8+ immune cells populations. | 500 mg/kg | Ayeka et al., 2017 |
| Licorice flavonoid oil | Body balance control by clinical trial | Activates AMPK in muscle cells, significantly decrease BMI and percentage of body. | 300 mg capsule daily for 16 weeks | (Kimoshita et al., 2021)
| Phenolics | Antiviral activity (novel influenza A (H1N1)) | Inhibits neuraminidase isolated from influenza viral strain, H1N1, H9N2, novel H1N1 and oseltamivir-resistance novel H1N1 expressed in 293T cells. | 0.675 to 54 μg/ml | Dao et al., 2011 |
| Ammonium salt of Glycyrrhizic acid (Japanese encephalitis virus (JEV)) including Nakayama, P-20,778 and 821.564 X48. | Anti-HIV | Inhibited giant cell formation. Glycyrrhizin inhibited plaque formation in all the three strains used in the study. | 20 μg/ml | Hatano et al., 1988 |
| Glycyrrhizin (2) | Anti-viral activity (An in vitro studies) | Interfered with Epstein-Barr virus replication cycle. | 0.04 and 4.8 mM | Lin, 2003 |
| | Anti-asthmatic effect (An in vivo studies) | Suppress IL-4, IL-5 and IL-13, enhances IFN-γ, inhibit recruitment of eosinophils and mucus over production in mice with OVA-induced asthma. | 10, 20, and 40 mg/kg | Ma et al., 2013b |
| | Immunomodulatory effect | Significantly inhibited IL-1β, IL-3, IL-5, IL-6, IL-10, IL-12 (p40), IL-12 (p70) and IL-13, | 400, 80, 16 mg/L | Liu et al., 2014 |
| | Bleomycin induced pulmonary fibrosis (An in vivo studies) | Ameliorated bleomycin induced pulmonary fibrosis, attenuated bleomycin induced inflammation, oxidative stress, epithelial-mesenchymal transition and activated β-signaling pathway in the lungs. | 50, 100 and 200 mg/kg for 28 days | Gao et al., 2015 |
| | Anti-inflammatory activity (An in vitro and in vivo studies) | Bio-availability improved as an evidence from improved activity. | 20 and 40 mg/kg | Bernala et al., 2016 |
| | Anti-allergic through immunomodulation (An in vitro studies) | Stabilized mast cells decreased vascular permeability by inhibiting the expression of Orai1, Stim1 and TRPC1, which blocked extracellular Ca2+ influxes. | 100 mg/kg | Han et al., 2017 |
| | Anti-inflammatory, anti-oxidation and anti-fibrotic properties in pulmonary fibrosis | It weakened expression of TGF-β1 and the phosphorylation of its downstream target, Smad2. | 75 mg/kg | Zhang et al., 2017 |
| Glycyrrhetic acid | Anti-inflammatory (An in vitro and in vivo studies) | Inhibition of pro-inflammatory mediators rise like iNOS, COX-2, TNFa, IL-1β, IL-4, IL-5 and IL-6. | Various dose | Fouladi et al., 2019 |
| Glycyrrhizin (3) | Anti-inflammatory on lung injury (An in vivo studies) | Enhanced TNF-α and IL-1β level in the pleural exudates and lung tissues of carrageenan-treated mice. Avert the neutrophils penetration into the inflamed cells by diminishing upregulation of KCAM-1, activate NF-κB and STAT-3. | 10 mg/kg i.p. | Menegazzi et al., 2008 |
| | Anti-viral | Block entry of influenza virus into cell. | 1 and 0.5 mM | Wolkerstorfer et al., 2009 |
| | Anti-asthmatic effect (An in vivo studies) | Reduced OVA-specific IgE levels in serum and TH2 cytokine, IL-4, and IL-5 levels in | 10 mg/kg | Hocaoglu et al., 2011 |
| (continued on next page) | | | | |
### Table 2 (continued)

| Compounds                  | Pharmacological Functions                          | Mechanism                                                                 | Doses                        | Reference                                      |
|----------------------------|----------------------------------------------------|---------------------------------------------------------------------------|------------------------------|------------------------------------------------|
| Anti-inflammatory activity | Inhibits NF-κB activation, MAPK signal cascade     | 1 mM                                                                      | Schrofelbauer et al., 2009   |
|                            | stimulated by TLR9 and TLR4 agonists and blocked induction of pro-inflammatory mediators induced by the TLR. |                             |                              |                                                |
| Immunomodulatory effect    | Up-regulated the expression of CD40, CD86 and MHCII maturation on dendritic cells. Further, improve production of IL-12. | 0.1 to 200 µg/ml            | Borthar et al., 2012         |
| Antiviral and immune-stimulant activity (An in vitro and in vivo studies) | Inhibits cytopathic effect of DHV (Duck Hepatitis Virus) | 10 mg/kg                     | Soufi et al., 2012           |
| Acute lung injury (An in vitro studies) | Significantly decreased protein contents, inflammatory cells count, TNFα, IL-6, IL-α, MPO activity as well as expression of COX-2, INOS, and NF-κB. | 50 µg/kg via tail vein      | Lee et al., 2019              |
| Anti-viral effect against SARS COV2Vero E6 and 293T cells | Geese Lenti-S infection by inhibiting the S protein-mediated cell binding. | 0.5–5 mM                     | Li et al., 2021c              |
| Glycyrrhetic acid (6) and derivatives | Inhibit the main protease Mpro that blocks the SARS-CoV-2 replication. | 0.5–1 mg/mL                  | van de Sand et al., 2021     |
| Glycyrrhizic acid (2) and 18β-glycyrrhetinic acid (6) | Depressed granulation tissue formation, suppressed tuberculin reaction, depressed swelling. | 5 mg/kg                      | Finney and Somers, 1958       |
| Glycyrrhizic acid (2) and Glycyrrhetic acids (6) | Inhibits cytopathic effect (CPE), viral protein synthesis and replication stages of virus. | Different dose               | Balta et al., 2021            |
| Immunomodulatory and Anti-inflammatory potentials | Inhibits IL-1β, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12, IL-15, eotaxin, and TNF-α expression. | Various dose                 | Richard, 2021                |
| Anti-inflammatory activity (An in vitro studies) | Exhibits central anti-inflammatory activity. | 1 mg/kg                      | Anderson and Smith, 1961     |
| 18β-glycyrrhetinic acid (6) | Lower CD40, MHC-II levels, decreased T-cell proliferation and IFN-γ level. | 10 µg/gm                     | Ebrahimiherad et al., 2016   |
| Licochalcone (6) | Down regulated TNF-α, IL-6, and IL-1β levels. | 20, 40 and 80 mg/kg           | Chu et al., 2012              |
| Licochalcone E (6) | Decreased release of NO, PGE2, mRNA expression and secretion of IL-6, IL-10 and TNF-α. | 0.5 - 2 mg                   | Lee et al., 2013              |
| Licochalcone A (6) | Inhibits production of pro-inflammatory mediators and microglial activation by blocking the phosphorylation of ERK1/2 and NF-κB, p65 in BV-2 cells. Also, attenuates decreases in dopamine uptake and tyrosine hydroxylase-immunoreactive loss. | 0.625–2.5 µg/mL for 1 h      | Huang et al., 2017            |
| Anti-inflammatory activity in parkinson disease model | Inhibits the P. acnes-induced degradation of procaspase-1 to caspase-1(p10) and cleavage of pro-IL-1β to IL-1β in BMDMs and also reduces the secretion of IL-1β in BMDMs. | 1.25% or 2.5% in 20 µl in 3:1 mixture of acetone and olive oil through topical application | Yang et al., 2018 |
| Cancer immunotherapy | Down-regulates the IFN-γ-induced PD-L1 protein expression and membrane localization in human lung cancer cells. Decreases the apoptosis and proliferative inhibition of Jurkat T cells caused by IFN-γ-induced PD-L1 expressing in AS549 cells in the co-culture system. | 10 µM                        | Yuan et al., 2021             |
| Liquiritin (7) | Effective in acute lung injury (An in vivo studies) | Inhibited capsaicin and allyl isothiocyanate evoked TRPV1, TRPV1. Suppressed inflammation and activation of NF-κB signaling pathway in lung tissues. | 25, 50 and 100 mg/kg         | Liu et al., 2020 |
| Isoliquiritigenin (32) | Smooth muscle relaxant (An in vivo and in vitro studies) | Activated xGC, GMP/PKG signaling cascade, inhibited PDEs and through Ca<sup>2+</sup> channels released tracheal smooth muscles. | 5, 10 and 20 mg/kg           | Liu et al., 2008 |
| Anti-inflammatory activity (An in vivo and ex-vivo studies) | Inhibited NLRP3, activated AIM2 and ASC oligomerization. | Different dose               | Honda et al., 2014           |
| Isoliquiritigenin (32) and Naringenin | Increases the numbers of Treg cells in purified naive CD4<sup>+</sup> T cells stimulated by CD3 and CD28 antibody and TGFβ. | 0.3–30 µM/pmol for isoliquiritigenin and 3–200 µM for naringenin | Guo et al., 2015 |
| Isoliquiritigenin (32) | Anti-inflammatory | Suppressed lipid A-induced phosphorylation of cKit, Jnk, and p38 that decrease TNF-α and fibrosis-related gene expression. | 3–10 µM                     | Watanabe et al., 2016 |
| Licocoumarone | Pulmonary inflammation | Inhibit LPS-induced expression of cytokines including IL-1β, IL-6 and IL-10, without altering TNF-α at both mRNA and protein levels. | 0–50 µM                     | Wu et al., 2017 |

* Chemical structure of important compound are given in Fig. 1.
pro-inflammatory gene expression including inhibition of HSN1-induced formation of ROS and reduced activation of NFkB, JNK, and p38, redox-sensitive signaling events (Michaelis et al., 2011). In another study liquorice (including 18β-GA) was found to be effective against human RSV infection on airway epithelial cells mainly by preventing viral attachment, internalization, and by stimulating IFN secretion. (Feng-Yeh et al., 2013). A supportive study on G. glabra aqueous extract for novel antiviral medication was further established

### Table 3

| Herbal Formulation | Pharmacological Functions | Mechanism | Doses | Reference |
|--------------------|---------------------------|-----------|-------|-----------|
| Herbal mixture     | Anti-asthmatic activity (Clinical trial) | Decreased the severity of cough and night time awakenings. | 5 ml (Thrice daily for 5 days) | Javid et al., 2019 |
| He-Jie-Shen-Shi decoction | Effective against Corona virus disease | Regulated HIF-1, NOD-like receptor, TNF-α, T cell receptor, sphingolipid, PI3K-Akt, toll-like receptor, VEGF, Fox O and MAPK signaling pathways. | 200 mg (Thrice daily) | Hu et al., 2021 |
| Herbal Medicine Formula | Anti-asthmatic activity (An in vivo studies) | Identified potential biomarkers responsible for allergic asthma such as α-acetylcarnitine (L1), thromboxane B2 (L2), 10-HDHE (L10), and 5-HETE (L11). | 9.47 gm/kg (once daily for 22 days). | Yu et al., 2017 |
| Traditional herbal formulation | Anti-inflammatory activity | Decreased production of TARC, MDC, RANTES, and IL-8. Further, down-regulated the mRNA expression of TARC, MDC, RANTES and IL-8 induced by TNF-α and IFN-γ in a dose-dependent manner. | 125, 250, and 500 pg/ml | Jeong et al., 2015 |
| Igongsan | Anti-inflammatory activity | Regulated the activation of NF-κB and caspase-1 in LPS-stimulated mouse peritoneal macrophages. | 1 mg/ml | Kim et al., 2014 |
| Herbal mixture | Anti-influenza (Clinical trial) | Decreases IFN-α level. | 2.5 g (Thrice daily) | Nabeshima et al., 2012 |
| Herbal medicine | Anti-asthma | Inhibit production of IL-4, a key Th2 cytokine involved in allergic airway inflammation in asthma. | 4, 20, 100 and 500 μg/mL | Jayaprakasan et al., 2013 |
| Herbal combinations | Chronic obstructive pulmonary disease | Inhibit neutrophilic airway inflammation by regulating the expression of inflammatory cytokines and CXCL-2 by blocking the IL-17/STAT3 pathway. | 50, 100 and 200 mg/kg | Kim et al., 2020 |
| Combination of Glycyrrhizic acid, Vitamin C and Curcumin Saiboko | Effective immunomodulator anti-inflammatory agent against Coronavirus | Immunomodulator activity against CoV infections and inhibit the inflammatory response to avert the onset of cytokine storm. | In silico | Chen et al., 2020b |
| | Bronchial asthma | Inhibit lymphocyte proliferation and release of chemical mediators from PBMC. | 100 mg/kg | Taniguchi et al., 2000 |

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**Fig. 3.** Immunomodulators effects of *G. glabra* L.
Moving ahead a study further confirmed that *G. glabra* extract (60 mg/100 ml) was nontoxic to embryonated eggs and able to inhibit replication of Newcastle disease virus (NDV) (Omer et al., 2014). Similarly, another study further revealed the antiviral activity of methanol extract of *G. glabra* (300 µg/ml) leaves against NDV through in vivo experimentation (Ashraf et al., 2017). Subcutaneous immunization of mice with an immunostimulating complex containing Glabilox (a saponin rich fraction of *G. glabra*) and H7N1 influenza virus antigens induce high levels of humoral and cellular response. Further, chickens vaccinated with the same immunostimulating complex protected 100% of the animals after experimental infection with a homologous virus support Glabilox as a great promising safe and effective alternative adjuvants (Aleyuk et al., 2019). Additionally, a recent study claims liquorice as a promising source of novel antiviral compounds against tobacco mosaic virus (Parizipour and Shahriri, 2020). *G. glabra* are also considered as a adaptogens in prophylaxis and treatment of several viral respiratory infections (Pannosian and Brenderj, 2020). In a very recent study liquorice root membranes may be considered to be used to produce a biobased face mask to control COVID-19 spread (Chowdhury et al., 2021). Further recently a study demonstrated effects of crude liquorice extract against pigeon paramyxovirus type 1 (PMV-1) through series of experiments by cytometric analysis for expression of genes encoding IFN-γ and surface receptors on CD8+, CD4+ and CD8+ T cells (Dziewulska et al., 2018). An in silico docking studies on jaranol, glycyrrhizaisoflavone and isoliquiritigenin found to be inhibit the function of cPLA2 and sPLA2 in macrophages suggesting immunomodulatory functions (Avinash et al., 2021). In summary *G. glabra* induces macrophages and stimulate the immune response as an evidence from several study. Further, N-acetyl muramoyl peptide (glycyrrhizin derivative) has found to exhibit immune-stimulating efficiencies specially on influenza virus by suppression of viral replication (Huan et al., 2021). Recently, a group of researcher showed that ethanol extract of *G. glabra* containing polysaccharides enhances the immunity through elevating the extents of serum IgG, IgM and IgA as well as by enhancing the prevalence of the lymphocytes in the spleen (Ng et al., 2021). Similarly, hydroalcohol extract of *G. glabra* and glycyrrhizic acid was found to significantly exhibits therapeutic and immunomodulatory activity as evidence from experiments on *L. major*-infected BALB/c mice (Sheikhi et al., 2021).

### Immunomodulatory activity

*G. glabra* was reviewed multiple time as a very cost effective and easily available immunomodulator (Fig. 3) as an evidence from several published studies (Kumar and Kumar, 2013; Tiwari et al., 2018). In an earlier study, highest immunological efficacy of mono extract of Glycyrrhiza and in combination with Echinacea was observed, when compared with Revitoniil (Wagner and Juric, 2002). Similarly, in another study purified polysaccharides obtained from *G. glabra* was found to modulate macrophage immune functions (Cheng et al., 2008). Further, immunostimulant effect of aqueous extract of *G. glabra* roots was observed with increased phagocytosis through carbon clearance test, haemagglutination antibody titre value and delayed type hypersensitivity at dose levels of 150 and 300 mg/kg of body weight (Bagherwal et al., 2009). Additionally, earlier findings suggest immunostimulating activity of polysaccharides obtained from *G. glabra* through elevation of IgG, IgM, and IgA level at blood serum of mice (Hong et al., 2009). Similarly, immunostimulant activity was observed after treatment of liquorice as an evidence from higher saliva IgA production (Katayama et al., 2011). In another study glycyrrhizin cause upregulation of CD40, CD86 and MHC-II expression, mainly responsible for maturation and function of mouse splenic DCs as an evidence from higher IL-12 production (Bordbar et al., 2012). Additionally, immunomodulatory activity of aqueous extract of *G. glabra* root at the dose 1.5 g/kg/body weight was demonstrated in combination with zinc through both in vitro and in vivo experiments (Mazumder et al., 2012). Immunomodulatory properties of the hydroalcohol extract of *G. glabra* roots was further assessed on Naval Medical Research Institute (NMRI)-mice model challenged with sheep red blood cells (SRBCs) suggested significant increase in the level of anti-SRBC antibody and thus improve immune system (Abtahifroushani et al., 2014). However, a research finding observed against immuno-stimulation (P > 0.05) by liquorice extract given with drinking water as an evidence from no any significant change on several immunological parameters tested for Influenza and Newcastle disease (Moradi et al., 2014). Progressively, another study suggested that promotion of regulatory T cell induction could be an underlying mechanism of liquorice action against autoimmune and inflammatory diseases (Guo et al., 2015). Similarly, a study on low molecular weight polysaccharides (obtained from *G. glabra*) against anticancer activity, suggested up-regulation of IL-7, which was responsible for proliferation and maturation of immune cells (Ayeka et al., 2016). Additionally, role of diet containing liquorice extract for growth and performance was further established (Elabd et al., 2016). Moreover, a study on polysaccharides (obtained from *G. glabra*) decreases TNFα and enhance the levels of IL-2, IL-6, IL-7 and serum antitumor cytokines (Ayeka et al., 2017). Further a combination containing *G. glabra* along with other plant found to exhibits immunopotentiating activity is through the modulation of biochemical factors, T-cell immunity, and transcription factors (Kaur et al., 2017). Progressively a study demonstrated usefulness of liquorice extract against pigeon paramyxovirus type 1 (PMV-1) through series of experiments by cytometric analysis for expression of genes encoding IFN-γ and surface receptors on CD8+, CD4+ and CD8+ T cells (Dziewulska et al., 2018). An in silico docking studies on jaranol, glycyrrhizaisoflavone and isoliquiritigenin found to be inhibit the function of cPLA2 and sPLA2 in macrophages suggesting immunomodulatory functions (Avinash et al., 2021). In summary *G. glabra* induces macrophages and stimulate the immune response as an evidence from several study. Further, N-acetyl muramoyl peptide (glycyrrhizin derivative) has found to exhibit immune-stimulating efficiencies specially on influenza virus by suppression of viral replication (Huan et al., 2021). Recently, a group of researcher showed that ethanol extract of *G. glabra* containing polysaccharides enhances the immunity through elevating the extents of serum IgG, IgM and IgA as well as by enhancing the prevalence of the lymphocytes in the spleen (Ng et al., 2021). Similarly, hydroalcohol extract of *G. glabra* and glycyrrhizic acid was found to significantly exhibits therapeutic and immunomodulatory activity as evidence from experiments on *L. major*-infected BALB/c mice (Sheikhi et al., 2021).

### Implication on COVID-19 infections

*G. glabra* and its active components have been shown promising results to combat SARS-CoV-2 infection and can be useful in treating patients with COVID-19 as on scientific evidences collected from some of the recently published reviews (Bailly and Vergoten, 2020; Fatima et al., 2020; Huacchco-Rojas et al., 2020; Jezova et al., 2020; Murck, 2020; Srivastava et al., 2020; Aditya et al., 2021; Boozari and Hosseinzadeh, 2021; Jalali et al., 2021; Khan et al., 2021; Idrees et al., 2021; Brendler et al., 2021; Diomede et al., 2021; Liana and Phanumartwiwath, 2021; Malekmohammad et al., 2021; Merarchi et al., 2021). Several mechanisms have been identified and have been depicted in Fig. 4. Moreover, several recent study on *G. glabra* in combination with standard therapies demonstrated significantly reduction of hospitalization rate and occurrence of COVID-19 symptoms (Armanini et al., 2020; Zhong et al., 2020; Gajewski et al., 2021; Li et al., 2021a; 2021b). Recently, several targets have been identified with the possible interaction of medicinal plants included liquorice as a hopeful therapeutic option for future drug (Bandyopadhyay et al., 2021; Shakhsi-Niaei et al., 2021; Tsai et al., 2021). Glycyrrhizin was studied well in past and found to be the most active molecule for inhibition of replication of the SARS-associated virus and can be utilized for treatment of SARS -associated coronavirus (Cinatl et al., 2003). Further, glycyrrhizin was considered as antiviral therapy through the inhibition of replication, penetration, and adsorption of SARS-CoV virus (Ng et al., 2021). Similarly, in a very recent study, glycyrrhizin obtained from *G. glabra* was evaluated on patients, infected with SARS-CoV prevents the replication of the SARS-CoV virus that adversely affects the lungs and also act against influenza A virus (H5N1) (Yang et al., 2020). Moreover, glycyrrhizin was also found to influences the cellular signaling pathway, incorporating transcription factors, casein kinase II and protein kinase C (Man et al., 2020). Recently, it was further postulated that tripterpenoids (glycyrrhizin and glycyrrhetinic acid) present in liquorice is able to inhibit several viruses growth including SARS-CoV-2. These compounds have ability to inhibit replication of virus, reactive oxygen species formation, β-chemokines, inflammation mediated by HMGB1/TLR4 and reduction in the binding of HMGB1 to DNA (Huan et al., 2021). Chinese traditional medicinal system (CTMS) has suggested use of glycyrrhizin (Ghannad et al., 2014).
may be emphatic agent against the COVID-19 pandemic. Even though their unavailability of appropriate reports proves its authenticity against the COVID-19. Nevertheless the CTMS recommends other kinds of herbal remedial constituents along with glycyrrhizin. Glycyrrhizin has been prescribed by CTMS, 80 ml/day for 7 days, and 40 ml/day for 4 days for attaining antiviral properties (Jitsuiki et al., 2020). ACE-2 is considered an active receptor to which the SARS-CoV virus can adhere. It is proved from scientific reports that curtailing the extents of ACE-2 can decrease the range of entry ways for the virus to the body during the beginning of initiation of infection and further dissemination to the inner part of the body (Huan et al., 2020). Medicinal utilization of glycyrrhizin for overcoming the COVID-19 has been proceeding effective through the mechanism that involving with ACE-2. Therefore alleviating the protection of ACE-2, also obstructing the thrombin, reactive oxygen species, reducing the pro-inflammatory cytokines, and aggravating the endogenous interferons (INF) (Anand et al., 2021). Therefore glycyrrhizin regulates the levels of T1h1/T1h2 cells and reduces the asthma in mice (Ishimaru et al., 2019; Samareh Fekri et al., 2021; Wahab et al., 2021). It is evidenced that glycyrrhizin regulates the levels of T1h1/T1h2 cells and reduces the asthma in mice (Ishimaru et al., 2019; Samareh Fekri et al., 2021; Wahab et al., 2021). It is evidenced that glycyrrhizin regulates the levels of T1h1/T1h2 cells and reduces the asthma in mice (Ishimaru et al., 2019; Samareh Fekri et al., 2021; Wahab et al., 2021).

**Antiasthmatic and antitussive activity**

*G. glabra* and its bioactive components glycyrrhizic acid have been documented and reviewed several time for prevention and treatment of respiratory tract inflammation including symptoms related to cough, cold and asthma (Aliavi et al., 2002; Honarmand et al., 2016; Langer et al., 2016; Chakotiya et al., 2017; Javadi et al., 2017; Fouladi et al., 2019; Ishimaru et al., 2019; Samareh Fekri et al., 2021; Wahab et al., 2021). A polymeric formulation developed from *G. glabra* given orally in Guinea pigs at dose of 50 mg/kg/bw reduced the amount of citric acid-activated cough efforts compared to codeine (Saha et al., 2011). Granules developed from the extract of *G. glabra* in SO2 gas-induced cough in mice have shown considerable results at 200 mg/kg/bw dose by suppressing the cough reflex compared i.e. around 47.13% in comparison with codeine sulfate (Shitole and Pawar, 2019). A study finds out liquiritin apioside and liquiritin as the major antitussive and expectorant compounds of liquorice through both peripheral and central mechanisms (Ruang et al., 2018).

**Pharmacokinetic profile**

In a very recent study on pharmacokinetic profiling of compound such as 7,4′-dihydroxylavone, formononetin, 3-R-glabridin, isoliquiritigenin, liquiritin, naringenin 5-O-glucoside, 3,3′,4,4′-tetrahydroxy-2-methoxychalcone, liquiritinapioside, isoliquiritigenin-4′-5β-o-apiosylglucoside and isoliquiritigenin-4-O-5β-o-apiosylglucoside. It was found that out of them glabridin and 7-hydroxy-4′-methoxyisoflavone exhibits 100% of oral absorption to develop orally active direct FXa inhibitors (Ibrahim et al., 2021).

**Clinical trial**

Several clinical trial on *G. glabra* have been recently reported for therapeutic regimen against COVID-19 patients. In brief, single center randomized open level trial (without any placebo and blinding control) was designed on patients including both male and female to investigate...
anti-inflammatory effect of *G. glabra* root extract. Trial investigated recovery rate, sign of adverse effect and time of improvement from major clinical symptoms (dry cough, fever and tiredness) and paraclinical features (lympho and thrombocytopenia) within seven days of randomization (Safa et al., 2020). A supportive clinical trial on 78-year-old man with accidental case having COVID-19 positive and acute respiratory distress symptoms speedily recovered after receiving liquorice along with intravenous immunoglobulin (Jitsukii et al., 2020). Further, formulations containing *G. glabra* through randomized clinical trial study on 36 chronic asthma patients, with 3.5 mg/kg dose in 200 ml of water have provided favorable amelioration in pulmonary functions, as that of (0.15 mg/kg) of Prednisolone. Similarly, hydroethanol crude extract of liquorice at 100 mg/kg imparted the same results as shown by Prednisolone as an oral dose of 10 mg/kg (Silveira et al., 2020). In another trial investigating efficacy of herbal extract for improving innate immunity of COVID-19 infected patients. Evidence on the basis of declining viral load at 4th day of treatment and early recovery was assessed (Rangnekar et al., 2020).

Toxicological studies

Methanol extracts of *G. glabra* root obtained from various geographical location (total: 9 samples) were investigated for cytotoxicity study against immortal human keratinocyte (HaCaT), liver carcinoma (HepG2) and lung adenocarcinoma (A549) cell lines using the *in vitro* 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium-bromide cell toxicity/viability assay. Considerable variations in cytotoxicity levels were observed among all tested samples of *G. glabra* (Basar et al., 2015). Moreover, *G. glabra* and glycyrrhizin salts are moderately toxic according to the LD50 have been reviewed. Single-dose at 1000 mg/kg/day not causes any death in female albino rats, but reduces attentiveness, touch sense, and locomotor function for 3 h (Nazari et al., 2017).

Conclusion and future perspectives

*G. glabra* is an abundantly used leguminous plant and its roots are utilized for medicinal purposes globally and also availed as a widely used sweetening agent as well as a flavoring agent by industries. It has been reported that more than 400 phytoconstituents have been merged out from the genus Glycyrrhiza and used therapeutically. Glycyrrhizin and glycyrrhizic acid are the leading and characteristic chemical constituents of liquorice, are liable for the sweet taste. Certainly *G. glabra* have been widely researched and found to be effective remedies as anti-inflammatory, antivirals and immunomodulation. Past and current research forced *G. glabra* and its active phytoconstituents to be effective against COVID-19 and any such future situation based on evidence. Therefore, the current study designed to deliver a content to be useful for development of future medicine and development of multiple value added product. Literature search reveal total 3908 articles including *G. glabra* as keywords are scrutinized for the requirement of current topic and out of them 198 are included in current study to finally deliver the content. Specifically, to establish liquorice and its bioactive compounds through research and review article for delivering anti-inflammatory, antivirals and immunomodulatory action is established by including several molecular mechanisms. Besides this liquorice plant has versatile therapeutic effects for the cure of many kinds of illness and also vast scope for future concerns for the treatment of various kinds of ailments including viral and immunity suppressant based infectious diseases.

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Authors agreement

Manuscript title: “Revisiting liquorice (*Glycyrrhiza glabra*) as antivirals and immunomodulators: potential pharmacological applications with mechanistic insight”. We, the undersigning authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons, who satisfied the criteria for authorship, but are not listed.

We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

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