Brief report on the HMGB1-antagonism exerted by glycyrrhizin could be fruitful against COVID-19

Giorgio Ciprandi1, Maria Luisa Bellussi2, Valerio Damiani3, Desiderio Passali2

1Consultant Allergist, Casa di Cura Villa Montallegro, Genoa, Italy; 2International Federation ORL Societies (IFOS) Executive Board members Rome Italy; 3Medical Department, DMG Italia, Rome, Italy.

Abstract. The COVID-19 pandemic era is causing a relevant issue for the health. There is no specific drug able to antagonize the SARS-CoV-2 infection. As a consequence, there is growing interest about potential molecules able to contrast infection. In this regard, HMGB, an alarmin, may play a relevant role in pathogenic mechanisms induced by SARS-CoV-2. As HMGB1 is antagonized by glycyrrhizin, this substance could be potentially useful as ancillary treatment in COVID-19. (www.actabiomedica.it)

Keywords: COVID-19, SARS CoV-2, HMGB1, Glycyrrhizic acid, Prophylaxis.

The pandemic COVID-19 has so far affected around 220 million confirmed patients, and nearly 4.5 million people have died worldwide as at 30 August 2021 (1). SARS-CoV-2, a single-strand-RNA coronavirus, is the pathogen for COVID-19. SARS-CoV-2 uses the ACE2 receptor as a gateway to enter the human cell, as its protein S can bind this cellular receptor (2). Once inside the cell, SARS-CoV-2 begins the replication phase, usually in the respiratory system, but also in digestive and nervous system, inducing a defensive host’s immune response. However, some patients (about 5-10%) break out in severe disease, they frequently have associated comorbidities, including obesity, hypertension, diabetes mellitus, and old age. These conditions are characterized by a low-grade chronic inflammation that may amplify the immune response against the virus, such as the cytokine storm syndrome, characterized by an overproduction of pro-inflammatory cytokines, including tumor necrosis factors, interleukins, and chemokines (2). The overproduction of these factors leads to severe tissue damage, progressing rapidly towards acute respiratory distress (ARDS), sepsis, multi-organ failure, and disseminated intravascular coagulation.

At present, a mass vaccination program is ongoing (August 2021) as there is no specific drug to treat COVID-19. In this regard, HMGB, an alarmin, may play a relevant role in pathogenic mechanisms induced by SARS-CoV-2. As HMGB1 is antagonized by glycyrrhizin, this substance could be potentially useful as ancillary treatment in COVID-19. (www.actabiomedica.it)
TLR is deeply involved in many respiratory infections, including influenza, bronchiolitis caused by the human respiratory syncytial virus, bacterial pneumonia, and acute lung injury (10). In particular, RAGE, a member of the immunoglobulin superfamily, may be involved in acute lung and systemic inflammatory events in severe COVID-19 patients (11). Also, severe COVID-19 patients express high HMGB1 levels (9). Noticeably, HMGB1 may promote a cytokine storm via TLR interaction and increase ACE2 expression through RAGE stimulation in COVID-19 patients (12).

Based on this background, HMGB1 could be an attractive target in treating COVID-19 (13). In this regard, an innovative approach glimpses the use of a saponin phytochemical: glycyrrhizin (14). The term saponin derives from the plant Saponaria officinalis that was used as a natural soap to wash the wool.

Glycyrrhizin is a triterpene saponin extracted from the root of the Glycyrrhiza glabra plant, typically cultivated in Europe. The term glycyrhiza derives from the old Greek as means γλυκύς (sweet) and ριζα (root). The main constituent of roots is glycyrhizin, a triterpenoid saponin that is almost 50 times sweeter than sucrose, being the primary active ingredient (15). Glycyrrhizin represents about 10% of the liquorice root dry weight, being a mixture of potassium, calcium, and magnesium salts of glycyrhizic acid that varies between 2% and 25% (16). After oral administration, glycyrhizin is metabolized to 18-glycyrrhetic acid 3-omono-glucuronide and glycyrrhetic acid by intestinal bacteria (15). Licorice is typically the main source of intake; however, also white walnut and cicely are foods rich in glycyrhizin.

Glycyrhrizin is a component of traditional Chinese medicine and boasts a millennial tradition in Western popular medicine (17). The perennial appeal relies on the broad mechanisms of action, including anti-inflammatory, antioxidant, corticosteroidal, antiallergic, antiviral, antimalarial, antihyperglycemic, antitussive, immunostimulating, and anti-HIV activity (18). For these reasons, glycyrhizin has been popularly used to treat many diseases, such as stomach ulcers, heartburn, acidity, flatulence, constipation, fever, cough, respiratory infections, asthma, and jaundice (19). The recommended daily dosage is about 5-10 grams of pulverized root (corresponding to about 200-400 mg of glycyrhizin) per os. However, there is accumulating evidence that glycyrhizin has been used as a true drug for treating liver diseases, mainly concerning chronic hepatitis, for more than 40 years, at the same posology. The rationale for this use depended on the documented activities, such as the inhibitory effect on pro-inflammatory cytokines, activation of CD8+ T cells, and proliferation of T regulatory cells (20).

Concerning COVID-19, as specific treatments are still lacking, glycyrhizin could potentially prevent and/or contrast SARS-CoV-2 infection. A recent paper summarized the multiple mechanisms through which glycyrhizin could be beneficial for COVID-19. Glycyrrhizin binds to ACE2, so diminishing the viral docking, downregulates pro-inflammatory cytokines release, and upregulates expression of anti-inflammatory mediators acting as a corticosteroid (21). Namely, the glycyrhizin/RAGE axis promotes or inhibits the nuclear factors’ activity so suppressing or enhance the immune response. Glycyrhizin actually has a steroid-like molecular structure and also exerts mild mineral active activity. However, glycyrhizin does not provide the classical adverse events associated with corticosteroid use. Therefore, glycyrhizin could be administered for longer periods than corticosteroids. Also, glycyrhizin inhibits the formation of reactive oxygen species consequent to viral infection so exerting antioxidant activity. Glycyrhizin is a selective inhibitor of thrombin and consequently could block the activation of the coagulation and complement cascade. Glycyrhizin also inhibits the MUC5AC gene transcription involved in mucus production, so that reduces mucus hypersecretion. Glycyrhizin fosters the production of interferon so increasing type 1 immune response against viral infection. In addition to these mechanisms of action, glycyrhizin has a specific activity on HMGB1. Glycyrrhizin physically binds to HMGB1 (trapping) to inhibit the interaction between HMGB1 and its receptors RAGE and TLR. Glycyrrhizin de facto sequesters extracellular HMGB1 inhibiting its intranuclear translocation. Consequently, glycyrhizin induces a relevant anti-inflammatory activity, so damping inflammatory phenomena dependent on innate immunity stimulation by viral infection (13). As HMGB1 is an alarmin, its effects are systemic, such as targeted towards many organs. HMGB1 inhibition
could be, therefore, an intriguing strategy to contrast viral infection. Thanks to the optimal safety profile, glycyrrhizin could be envisaged as a multi-target compound able to fight viral disease.

From a practical point of view, glycyrrhizin is available in different oral formulations, including tablets, elixir, syrups, or for topical administration (dipotassium glycyrrhizinate), such as nasal spray, eye drops, and mouthwash, combined with other natural substances, for example, zinc, vitamin D, hyaluronate, and lactoferrin. These substances can have synergic antiviral activities.

In conclusion, glycyrrhizin is an interesting phytochemical provided by multifaceted antiviral and anti-inflammatory activities and good safety and tolerability. In particular, there is growing interest about this molecule as documented by the several reviews, and in silico and in vitro evidence recently published (22-28). It has also been hypothesized the use of saponins as adjuvants for the COVID-19 vaccines (29). Nevertheless, there is the need to further studies that document the real beneficial effect of glycyrrhizin in the treatment (or even prevention) of COVID-19. In this regard, a retrospective observational investigated the use of giammonium glycyrrhizinate and vitamin C in patients with COVID-19. This multicomponent compound reduced the incidence of acute respiratory distress syndrome (30). However, we are still waiting for a randomized controlled study that provide documented evidence.

Competing Interests: None but for VD who is an employee of DMG Italia.

Authors’ contribution: all authors contributed to this paper, read, and approved the final version.

References

1. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int
2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020;324(8):782-793
3. Marmitt DJ, Goettet MI, Rempel C. Compounds of plants with activity against SARS-CoV-2 targets. Expert Rev Clin Pharmacol 2021 (in press)
4. Omrani M, Keshavarz M, Ebrahimi SN, Mehrabi M, McGraw LJ, Abdalla MA, et al. Potential natural products against respiratory viruses. A prospective to develop anti-COVID-19 medicines. Frontiers Pharmacol 2021;11:586993
5. Koyama S, Kondo K, Ueha R, Kashiwadani H, Heinbockel T. Possible Use of Phytochemicals for Recovery from COVID-19-Induced Anosmia and Ageusia. Int J Mol Sci 2021;22(16):8912
6. Rehman MFU, Akhter S, Batool AI, Selamoglu Z, Sevindik M, Eman R, et al. Effectiveness of Natural Antioxidants against SARS-CoV-2: Insights from the In-Silico World. Antibiotics (Basel). 2021 (in press)
7. Shah MA, Rasul A, Yousaf R, Haris M, Faheem HI, Hamid A, et al. Combination of natural antivirals and potent immune invigigators: A natural remedy to combat COVID-19. Phytother Res 2021 (in press)
8. Qu L, Chen C, Chen Y, Li Y, Fang H, Huang H, et al. High-mobility group box 1 (HMGB1) and autophagy in acute lung injury (ALI): a review. Med Sci Monit 2019;25:1828-1837
9. Yang H, Wang H, Andersson U. Targeting inflammation driven by HMGB1. Frontiers Immunol 2020;11:484
10. Andersson U, Ottestad W, Tracey KJ. Extracellular HMGB1: a therapeutic target in severe pulmonary inflammation including COVID-19? Mol Med 2020;26:42
11. Chiappalupi S, Salvadori L, Vukasinovic A, Donato R, Sorci G, Ruzzii F. Targeting RAGE to prevent SARS-CoV-2-mediated multiple organ failure: hypotheses and perspectives. Life Sci 2021;272:119251
12. Chen R, Huang Y, Quan J, Liu J, Wang H, Billiar TR, et al. HMGB1 as a potential biomarker and therapeutic target for severe COVID-19. Heliyon 2020;6:e05672
13. Bailly C, Vergoten G. Glycyrrhizin: an alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome? Pharmacol Therap 2020;214:107618
14. Merarchi M, Dudha N, Capodaglio G, Piccolo O. A new exploration of licorice metabolome. Food Chemistry 2017;221:939–948
15. Richard SA. Exploring the pivotal immunomodulatory and anti-inflammatory potentials of glycyrrhizic and glycyrrhetic acids. Mediators Inflamm 2018;2018;32(12):2323-2339
16. El-Saber Batiha G, Beshbishy AM, El-Mleeh A, Abdel-Daim MM, Prasad Devkota H. Traditional uses, bioactive chemical constituents, and pharmacological and
toxicological activities of *Glycyrrhiza glabra* L. (Fabaceae). Biomolecules 2020;10:352
20. Murck H. Symptomatic protective action of glycyrrhizin (Licorice) in COVID-19 infection? Frontiers Immunol 2020;11:1239
21. Luo P, Liu D, Li J. Pharmacological perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19. Int J Antimicrob Agents 2020;55.105995
22. Narkhede RR, Pise AV, Cheke RS, Shinde SD. Recognition of Natural Products as Potential Inhibitors of COVID-19 Main Protease (Mpro): In-Silico Evidences. Nat Prod Bio-prospect. 2020;10(5):297-306
23. Singh M, Trivedi D, Mohapatra R, Bagchi T, Durthi CSP, Kuppam C. Phytotherapeutic Drugs For Covid19 Treatment: A Scoping Review. Curr Pharm Des. 2021 (in press)
24. Tang C, Ding H, Sun Y, Han Z, Kong L. A narrative review of COVID-19: magnesium isoglycyrrhizinate as a potential adjuvant treatment. Ann Palliat Med. 2021;10(4):4777–4798
25. Al-Kamel H, Grundmann O. Glycyrrhizin as a Potential Treatment for the Novel Coronavirus (COVID-19). Mini Rev Med Chem. 2021 (in press)
26. Zhao Z, Xiao Y, Xu L, Liu Y, Jiang G, Wang W, et al. Glycyrrhizic Acid Nanoparticles as Antiviral and Anti-inflammatory Agents for COVID-19 Treatment. ACS Appl Mater Interfaces. 2021;13(18):20995-21006
27. van de Sand L, Bormann M, Alt M, Schipper L, Heilingloh CS, Steinmann E, et al. Glycyrrhizin Effectively Inhibits SARS-CoV-2 Replication by Inhibiting the Viral Main Protease. Viruses. 2021;13(4):609
28. Gowda P, Patrick S, Joshi SD, Kumawat RK, Sen E. Glycyrrhizin prevents SARS-CoV-2 S1 and Orf3a induced high mobility group box 1 (HMGB1) release and inhibits viral replication. Cytokine. 2021;142:155496
29. Sharma R, Palanisamy A, Dhama K, Mal G, Singh B, Singh KP. Exploring the possible use of saponin adjuvants in COVID-19 vaccine. Hum Vaccin Immunother. 2020;16(12):2944–2953
30. Tan R, Xiang X, Chen W, Yang Z, Hu W, Qu H, et al. Efficacy of diammonium glycyrrhizinate combined with vitamin C for treating hospitalized COVID-19 patients: a retrospective, observational study. QJM. 2021 (in press)

**Correspondence:**
Received: 30 August 2021
Accepted: 4 September 2021
Giorgio Ciprandi
Via P. Boselli 5, 16146 Genoa, Italy
E-mail: gio.cip@libero.it