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Research Article

Glycyrrhizic Acid as a Potential Cost-Effective Botanical Drug for Pandemic SARS-Cov-2 Infection Prophylaxis

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Abstract: Counties mitigate the virus through interventions like home isolation and social distance affected economic downward. So far no treatment or vaccine has been conformed, making people in depressed and anxious physiological mind state from catching the virus themselves or their beloved ones. Also, with number of infected individuals are rising, the health system is becoming overwhelmed. Preventing the disease and preventing its occurrence by taking a prophylaxis has a great effect in reducing the negative consequences of this disease, including huge human and economic losses, even on the psychological level, and reducing the isolation period. Glycyrrhizin acid is the main active component of Licorice root which has been known in traditional Chinese and Japanese medicine since ancient times. In these cultures, glycyrrhizin acid (GA) is one of the most frequently used drugs. The potential of GA to prevent or control the disease caused by this disease primarily from its ability to inhibit the enzyme 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1). the consumption of GA has various benefits including antiviral, anti-inflammatory, antioxidant and immunomodulation effect. In this review we propose Glycyrrhizic acid as a potential cost-effective botanical drug for pandemic SARS-COV-2 infection prophylaxis.

Keywords: Antiviral;Anti-inflammatory; Antioxidant; Botanical drugs; Immunomodulator; Glycyrrhizic acid; Licorice; SARS-COV-2, Pandemic, Prophylaxis.

INTRODUCTION

SARS-CoV-2 is the seventh member of the family of CoVs that infect humans. Four human CoVs (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) are able to cause a wide range of upper respiratory tract infections (common cold), whereas SARS-CoV and MERS-CoV are responsible for atypical pneumonia. The causes of different infection sites are likely related to the presence of dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2) in the lower respiratory tract, which are the major human receptors for the surface spike (S) glycoprotein of MERS-CoV and SARS-CoV, respectively (Paules *et al*., 2020) (Raj *et al*., 2013) (Kuba *et al*., 2005). The genetic sequence of SARS-CoV-2 is ≥70% similar to that SARS-CoV, and SARS-CoV-2 is capable of using the same cell entry receptor (ACE2) as SARS-CoV-1 to infect humans (Hui *et al*., 2020) (Zhou *et al*., 2020). However, there are more differences in the key S proteins that the viruses use to interact with host cells. SARS-CoV-2 spike binds to human ACE2 with approximately 10–20-fold higher affinity than the SARS-CoV-1 spike (Wrapp *et al*., 2020), making it easier to spread from human to human. Upon entry into alveolar epithelial cells, SARS-CoV-2 replicates rapidly and triggers a strong immune response, resulting in cytokine storm syndromes and pulmonary tissue damage. Immunization keeps people healthy and ensures retention of healthcare resources (Whitney *et al*., 2014). There are many economic and societal values of prophylaxis. These include outcome-related productivity gains (improved cognition and physical strength, as well as school enrolment, attendance, and attainment), behaviour-related productivity gains (influence on fertility and consumption choices), and community externalities (herd effect, indirect protection, prevention of antibiotic resistance) among others (Bärnighausen *et al*., 2011) (Beutels, 2002).

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Glycyrrhizic acid is an oleanane type triterpenoid saponin, conjugate of two molecules, namely glucuronic acid and glycyrrhetinic acid. It is naturally extracted from the roots of licorice plants. Glycyrrhizic acid producing species are Glycyrrhiza glabra L., G. uralensis Fisch. and G. inflata Batal. It has a sweetness associated with a characteristic licorice taste, sometimes described as "cooling". With no calorific value and a sweetness of about 50 times that of sucrose. GA inhibit the enzyme 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1). However, this action is non-selective, as GA also inhibits the other isoform of this enzyme, 11β-HSD2 (Isbrucker & Burdock, 2006). The two isoforms of 11β-HSD have been shown to have opposing functions, which is of vital consequence with regards to the effects of GA consumption. 11β-HSD2 is a dehydrogenase that catalyzes the reversible conversion of active glucocorticoids (corticosterone in rats, cortisol in humans) to their inactive derivatives (11β-dehydrocorticosterone in rats, cortisone in humans). On the other hand, 11β-HSD1 can act both as a dehydrogenase, to catalyze the deactivation of glucocorticoids, as well as a reductase, to catalyze the activation of glucocorticoids (Ploeger *et al*., 2000) (Tomlinson & Stewart, 2005). In intact cells, the reductase actions of 11β-HSD1 that result in glucocorticoid activation have been shown to be more potent than their dehydrogenase actions (Ploeger *et al*., 2000). Has been reported to have multiple therapeutic properties like anti-inflammatory, anti-ulcer, anti-allergic, antioxidant, anti-tumor, anti-diabetic, hepatoprotective, treatment of premenstrual syndrome and viral infections (Ming, L.*et al*., 2013).

At this review we will discuss the cost-effective of using Glycyrrhizic acid as botanical drug prophylaxis for pandemic SARS-COV-2 infection depending on the pathology and the published clinical trials.

DISCUSSION

Glycyrrhizic acid shows significant anti-inflammatory activity and alleviates inflammatory lung disease by reducing the cytokine production via the phosphatidylinositol 3-kinase/Akt/glycogen synthase kinase-3-beta (PI3k/Akt/GSK3β) pathways. Glycyrrhizic acid can be converted into 18β-glycyrrhetinic acid before entering the circulatory system that leads to the dissociation of a glucocorticoid receptor (GR)-HSP90 complex to block inflammation (Kao, C.*et al* .,2010).Reducing cytokine production is crucial since COVID-19 patients suffer from cytokine storm (Yaling ,S. *et al*. ,2020).It has been shown that GA can promote function of endothelial system and secretion of cytokines such as interleukin- (IL-) 1 and interferon- (IFN-) α (Hua *et al*., 2012), induce maturation of dendritic cells (DCs) (Bordbar *et al*., 2012), increase T cells proliferation and production of IL-2 and IFN-γ (Zhang *et al*., 1993) (Abe *et al*., 1982), augment natural killer (NK) cell activity (Itoh K., 1983), enhance phagocytic capacity and nitric oxide (NO) production in activated macrophages (Yi *et al*., 1996), and downregulate the production of IL-8 and eotaxin-1 in human lung fibroblast cells (Matsui *et al*., 2004). These studies indicated that GA may serve as an immune modulator which precisely regulates the cellular immunity.

Study noticed treatment with Glycyrrhizic acid caused the total white blood cells (WBC) count, bone marrow cellularity and α-esterase positive cells to be enhanced. Treatment along with antigen produced an enhancement in the specific antibody titer and the number of plaque forming cells (PFC) in the spleen. Remarkably inhibited delayed type hypersensitivity reaction (DTH). These results indicate the immunomodulatory activity of Glycyrrhizic acid (Raphael, J.*et al*., 2003).

Glycyrrhizic acid has proved to be antioxidant through many studies .One of the study was conducted on the effect of Glycyrrhizic acid on Isoproterenol which cause the imbalance between oxidants and antioxidants in the myocardium and accumulations of free radicals leading to the onset of acute coronary syndrome. Glycyrrhizic acid exhibited a positive effect against isoproterenol. At the same time, it has been proven to be a powerful antioxidant that decreases myocardial lipid hydroperoxide and 8-isoprostane levels (Haleagrahara, N.*et al*., 2011). Furthermore, the supramolecular complexes of carotenoids with Glycyrrhizic acid were found to exhibit scavenging activity toward hydroperoxyl (OOH) radicals that was ten times (**10×**) stronger than that of carotenoids alone (Polyakov, E, *et al*.,2006). Interestingly study found Glycyrrhizic acid protected the cellular DNA from radiation-induced strand breaks in a concentration-dependent manner proving the radical scavenger action of Glycyrrhizic acid (Gandhi, N.*et al*., 2014). The oxidative properties of Glycyrrhizic acid are important, taking into consideration that patients infected with coronavirus 2 deal with oxidative stress (Kouhpayeh, S.*et al*., 2020).

Also adding the Glycyrrhizic acid effect on renin-angiotensin-aldosterone system. By inhibiting 11β-hydroxysteroid dehydrogenase that converts cortisol to cortisone leading to Renin production suppression, the formation of angiotensin I is not stimulated, and aldosterone suppression. It can cause hyper-mineralocorticoidism (Størmer, C.*et al*., 1993). In tissues that are targeted significantly by aldosterone, such as the kidneys, which have an abundance of mineralocorticoid receptors (Ploeger *et al*., 2000). As the affinity of mineralocorticoid receptors for glucocorticoids and aldosterone is similar, the presence of higher concentrations of active glucocorticoids—as occurs with GA-induced suppression of 11β-HSD 2

(Van Uum *et al*., 1998)—could lead to their competitive binding to mineralocorticoid receptors, leading to a syndrome of apparent mineralocorticoid excess (Van Uum *et al*., 1998) (Sheppard & Funder, 1987). This is presented in the form of sodium and water retention and potassium secretion, that also responsible to cause side effects edema and hypertension (Van Uum *et al*., 1998). This can also depress the renin-angiotensin aldosterone system (RAAS) in order to compensate for the changes in water balance caused by fluctuations in electrolyte levels (Størmer *et al*., 1993).

The antiviral properties of Glycyrrhizic acid have been reported since seventies. Some of the examples; study showed inhibitory effect on vaccinia virus, Newcastle disease virus and vesicular stomatitis virus and inactivates herpes simplex virus irreversibly (Pompei, R.*et al*., 1980). Also, the antiviral effect of GA on the other viruses was further explored by using pseudorabies virus (PRV) and porcine epidemic diarrhea virus (PEDV) as a representative of herpes virus and coronavirus, respectively. The PRV is an enveloped, double-stranded DNA virus in the family Herpesviridae (Wong *et al*., 2019), while PEDV is a large-enveloped RNA virus in the genus, alphacoronavirus of the coronavirus family (C., 2015). GA Inhibit the Proliferation of Coronavirus and Herpesviridae, Importantly inhibitory effect on SARS-coronavirus (SARS-CoV) replication in vitro (Hoever, G.*et al*., 2005) which is a promising antiviral effect on COVID-19 patients since high genetic similarity between SARS-CoV-2 and SARS-CoV (Ahmed, F. *et al*., 2020).).

Having a prophylaxis against COVID-19 is really important to prevent our self and prevent it from spread and it will help in improve equality of life and bring life to it normal rhythm According to literature we can conclude that Glycyrrhizic acid has many benefits in regarding to SARS-COV-2 which can be use as botanical drug prophylaxis which may decrease number of infected people and decrease number of people who need hospital care and with less numbers of ICU patients needs.

CONCLUSION

In summary, we conclude that Glycyrrhizic acid play a major role in renin system that could prevent the virus from entering the body. Also, Glycyrrhizic acid has been reported for its antioxidant, anti-inflammatory properties and more which is a plus. So, we recommend use of Glycyrrhizic acid 1 gm (**equivalent to 2 capsules of standardized licorice extract of 500 mg strength**) twice daily as COVID-19 prophylaxis. We still we need a clinical trial to test Glycyrrhizic acid clinical usefulness.

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