Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Biomedicine & Pharmacotherapy 143 (2021) 112150

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Potential of herbal products in prevention and treatment of COVID-19. Literature review

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ARTICLE INFO

Keywords:
COVID-19
Coronavirus
Traditional Chinese medicine
Glycyrrhiza glabra
Pelargonium sidoides
Glycyrrhizin

ABSTRACT

The COVID-19 epidemic is the greatest pandemic that human kind experienced for decades, with high morbidity and mortality. Despite recent development of vaccines there is still many severe cases of COVID-19. Unfortunately there is still no standardized therapies and treatment of severe cases is very challenging. The aim of this study is to indicate if herbs administered alone or as a complementary therapy could be used as prophylaxis or treatment of SARS-CoV-2 infection. Over 85% of patients with COVID-19 in China used Traditional Chinese Medicine (TCM), and a most common herb is Glycyrrhiza glabra, which in vitro inhibits replication of different enveloped viruses, including coronaviruses. Glycyrrhizin in vitro connects and changes conformation of ACE2 receptors, which are vital for SARS-CoV-2 penetration into host cells. Pelargonium sidoides show immunomodulatory and antiviral properties in clinical and in vitro studies, and it inhibits replication of HCo-229E coronavirus. Glycyrrhiza glabra in combination with standard therapies significantly reduces the hospitalization rate and occurrence of COVID-19 symptoms. As complementary therapies lianhuaqingwen capsules and jinhua qinggan granules reduces hospitalization rates, time to symptoms recovery and improve patient psychological comfort. In view of SARS-CoV-2 other herbs are not effective, e.g. maxingshigan–yinqiaosan, or therapeutic concentration would be impossible to achieve, e.g. ephedra herb, or there is simply no proper data. Therefore, Liquorice and Pelargonium sidoides are effective against coronaviruses and could be possibly used as prophylaxis and treatment of COVID-19, while lianhuaqingwen capsules and jinhua qinggan granules can be useful as a complementary therapy to conventional treatment.

1. Introduction

The COVID-19 epidemic is the greatest pandemic that human kind experienced for decades. According to WHO till June 21, 2021, there were 178,118,597 confirmed cases of COVID-19 and 3,864,180 deaths in course of this disease worldwide [1]. Meta-analysis performed by Hu et al. show that 12.6–23.5% of COVID-19 cases are severe, and mortality ranges from 2% up to 4.4% confirming the gravity of this problem. The epidemic started in Wuhan, China, where SARS-CoV-2 was isolated for the first time on December 8, 2019, and from that time it spread all around the globe [2]. Regarding first appearance of SARS-CoV-2 it is not surprising that at the beginning of the pandemic most patients were Chinese. Interestingly, over 85% of patients with COVID-19 in China received Traditional Chinese Medicine (TCM) treatment at the top of conventional therapies [3]. Moreover, some provinces had their own guidelines for prevention and treatment of SARS-CoV-2 infection with TCM, and recommended medications differ according to the age of a patient and infection severity [4,5]. Meta-analysis performed by Luo et al. show that traditional Chinese herbal medicine reduced the risk of H1N1 infection in comparing to placebo, with relative risk 0.36 (95% CI 0.24–0.52). Moreover, among 16,437 health care workers from hospitals treating patients with SARS none of TCM group contracted SARS, while infection rate was 0.4% ($p = 0.035$) in non-herbal group [6]. However, typical TCM medications are not just one herb but mix of even dozens of different herbs, extracts, etc., therefore, even if treatment would be successful it is hard to indicate one active, beneficial component. This prompted Ang et al. to investigate TCM herbal mixes, and delineate its ingredients [5]. According to this study Chinese patients most commonly used Glycyrrhiza glabra root, and less frequently armeniacae semen amarum, ephedra herb and gypsum fibrosum [5].

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https://doi.org/10.1016/j.biopha.2021.112150
Received 28 June 2021; Received in revised form 27 August 2021; Accepted 31 August 2021
Available online 2 September 2021

Although a coronavirus pandemic appears to be something new and uncomprehended, similar epidemics occurred in the past, in example in 2003. Therefore, herbal medicines, not only TCM, such as Glycyrrhiza glabra and Pelargonium sidoides roots were investigated as a potential treatment of coronavirus infection. The aim of this study is to review available literature regarding herbal medications in view of coronavirus infections, in order to delineate if such therapies have a potential to cure SARS-CoV-2 infections or facilitate conventional treatment.

2. Results

Most important studies cited in this article are gathered in Table 1.

2.1. Glycyrrhiza glabra

2.1.1. General information

Liquorice (Glycyrrhiza glabra L.) is a perennial plant of the Fabaceae family commonly found in South-West Asia, Eurasia and the Mediterranean [7,8]. The raw material is made of shallow peeled and dried roots and runners of 3–4-year-old plants, harvested in autumn or early spring, although fresh roots is also used [7,8]. Liquorice contains the following active substances: Glycyrrhizinic acid (glycyrrhizin) and its salts – which is a substance with antiviral properties, other triterpene saponoside, flavonoids, coumarins, and carbohydrates [8].

2.1.2. Liquorice root extract as a potential COVID-19 treatment

The pharmacodynamics of glycyrrhizin in terms of viruses is still unknown, however, researches show that this substance through protein kinase C, casein kinase, AP-1 (activator protein 1), MAPK-p38 and the nuclear factor-κB, affects DNA repair and gene expression (Fig. 1) [9–12]. Moreover, glycyrrhizinic acid and its metabolite glycyrrhetinic acid inhibits the expression of induced nitric oxide synthase (iNOS) in macrophages, thereby decreasing the production of NO, which is an important mediator in the pathomechanism of acute lung injury [12]. In response to the detection of a new coronavirus (SARS-CV) causing severe acute respiratory distress syndrome (SARS), Cinatl et al. investigated the effects of various substances on its cytopathogenicity [9]. To this end, they isolated the virus from two patients admitted to the clinical center of the University of Frankfurt and applied the isolates to Vero cell cultures. After 72–96 h, researchers assessed the cytopathogenicity of the virus and the number of viable cells to assess the effectiveness of SARS-CV 50% virulence inhibition (EC_{50}) and the toxic dose of the drug that would damage 50% of Vero cells (CC_{50}). Ribavirin at a concentration of 1000 μg/ml did not affect virus development. In turn, for glycyrrhizin $EC_{50} = 300$ μg/ml, $CC_{50} > 20{,}000$ μg/ml, and thus the therapeutic index (TI) was > 67 (the concentration was maintained during and after virus adhesion) [9]. A similar study was conducted by Chen et al. [10]. Using the 39849 SARS coronavirus strain, researchers demonstrated that glycyrrhizin did not affect virulence and multiplication of the virus in fRhK-4 cell cultures. However, repetition of the test on the Vero E6 cell line showed that glycyrrhizin inhibits SARS-CV virulence and replication with $EC_{50} = 100$ μg/ml [10]. Although results of these studies are promising in view of COVID-19 it must be highlighted that only two virus isolates were used in the trial of Cinatl et al. and that in both studies researchers used isolates of SARS-CV not SARS-CoV-2, therefore, considering high mutagenicity of viruses the results may not apply to SARS-CoV-2.

This new type of coronavirus penetrates into the lung cells through the ACE 2 receptors with which it binds. In their recently published study, Chen and Du showed that glycyrrhizin has the ability to bind to ACE 2 at sites ARG-559, GLN-388, ARG-393, ASP-30 with $\Delta G = -9$ kcal/mol [11]. Due to this property, glycyrrhizin has the potential to block the entry of the virus into cells and the development of the disease, although more research is needed to confirm this.

Importantly, Zhao and colleagues have shown that glycyrrhizin protects the lungs and reduces mortality in rat sepsis model. Survival rates increased from 0% to 40% after dosing Sprague-Dawley individuals with 25 mg/kg of glycyrrhizin and up to 60% at 50 mg/kg. Researchers have found that glycyrrhizin reduces inflammation and leukocyte migration into the lungs, inhibits iNOS expression, reduces cell sensitivity to oxidative stress and inhibits apoptosis through transcription factors such as MAPK-p38 and reduction of nuclear factor κB activity. This effect was directly proportional to the dose of glycyrrhizin [12]. This indicates that LRE and glycyrrhizin may not only prevent infection but also alleviate its course and reduce mortality.

These studies show that glycyrrhizinic acid may be an effective drug in the fight against respiratory infections caused, among others, by coronaviruses, including SARS-CoV-2, however human trials and most importantly, trials with SARS-CoV-2 are needed in order to assess effectiveness of the glycyrrhizinic acid.

2.1.3. Pharmacokinetics

Despite the promising studies described above for liquorice root extract (LRE) antiviral properties, the use of liquorice in therapy is questionable because of its pharmacokinetics.

Chen et al. in their article report that after oral administration to healthy subjects of 100 mg of glycyrrhizin, it was not detected in the blood of the subjects, moreover, intravenous administration of 200 mg of glycyrrhizin resulted in achieving a maximum serum concentration of 80 μg/ml, which is less than the effective dose [10]. According to the authors, this may be related to the metabolism of glycyrrhizinic acid to glycyrrhetinic acid by intestinal bacteria and the rapid excretion of glycyrrhizin in the bile and urine. However, it is worth noticing that glycyrrhetinic acid also has antiviral properties, and its concentration was not measured [9]. Therefore, Chen et al. questioned the effectiveness of liquorice root therapy [10].

Jiang et al. investigated the pharmacokinetics of glycyrrhizin on mouse models to determine how it is affected by carbohydrates contained inter alia in honey. After administration to 8 Kunming mice with a mass of 30 ± 2 g of water with a glycyrrhizin concentration of 638 μg/ml, its maximum plasma concentration was 143.81 ± 19.34 μg/ml and was achieved within 45 ± 25.20 min [13].

Regarding aforementioned data, it appears that in order to obtain a maximum blood glycyrrhizin concentration of 100 μg/ml, approximately 15 mg/kg of glycyrrhizin should be administered. Extrapolating this information, it can be assumed that oral consumption of 1.05 g of glycyrrhizin by a man weighting 70 kg will allow to temporarily achieve therapeutic concentration. This dose corresponds to 26.25 g of herbal raw material, which should contain a minimum 4% of glycyrrhizinic acid. However, this dose exceeds the average daily intake recommended by the European Commission, it does not seem impossible or dangerous to achieve.

2.2. Pelargonium sidoides

2.2.1. General information

Pelargonium sidoides is a perennial plant of the Geraniaceae family commonly found in South Africa and Lesotho highlands, and is commonly named African geranium [14]. Pelargonium sidoides was used for centuries by indigenous habitants of Africa as a remedy for all kinds of conditions such as diarrhea, gastritis, common cold, upper respiratory tract infections, skin infections and tuberculosis. Peculiarly, due to its effectiveness against tuberculosis African geranium was brought to Europe at the end of the 19th century. After disclosure of proved cases of curing advanced tuberculosis with African geranium root extract, this agent was widely introduced in Europe as an experimental tuberculosis therapy [14]. The raw material of P. sidoides is made of fresh or dried roots [14]. P. sidoides contains the following active substances: anthocyanins, coumarins, gallic acid derivatives, flavonoids, tannins, phenols and hydroxycinnamic acid derivatives [14].

Table 1
Summary of selected reviewed studies.

Authors (year) [reference number]	Subjects	Intervention	results
Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., & Doerr, H. (2003), [9]	Vero cell lines with SARS isolates (2)	Incubation with Glycyrrhizin or antiviral drugs	Glycyrrhizin had the highest selectivity index no matter at which stage of viral replication was administered (> 33–> 67) and inhibited SARS virus replication most strongly. Glycyrrhizin was most effective when given both during and after the adsorption period (EC50 300 mg/L).
Chen, F. (2004), [10]	fRhK-4 and Vero E-6 cell lines with SARS isolates (10)	Glycyrrhizin and other antiviral drugs	No inhibitory activity in the cell line fRhK-4 for glycyrrhizin. Inhibitory activity in the Vero E-6 cell line (EC50 = 100 μg/ml)
Zhao, H., Zhao, M., Wang, Y., Li, F., & Zhang, Z. (2015), [12]	Rats. Sham operation group(6), glycyrrhetinic acid (GA) group (6), sepsis group (6), sepsis plus GA group (6), sepsis plus GA group – different doses of GA (6)	25 mg/kg,50 mg/kg Glycyrrhizic acid	GA increases the survival of rats with sepsis by 60% in 50 mg/kg group and by 40% in 25 mg/kg group. GA reverts the protein BALF content (25 mg/kg-0,6,p < 0,05; 50 mg/kg-0,4, p < 0001). GA decreases the Wet-to-dry ratio of lung. GA prevents the growth of multinuclear cells and reduces leukocyte apoptosis in vitro. GA inhibits NO and iNO expression. GA inhibits MDA production by 50%, reduces nitrotyrosine concentrations by 50%, increases Bcl-2/Bax ratio and p38MAPK activation.
Herbert Kolodziej, Oliver Kayser, Oliver A. Radtke, Albrecht F. Kiderlen, and Egon Koch (2003), [15]	murine L929 fibroblasts	Murine bone marrow-derived macrophages incubated for 48 h with test compounds (EPs® 7630, root extract) (50 μg/ml) or medium alone, exposed to EMCV suspension.	Prominent cytoprotective effects were observed for the root extract, as evident not only by complete inhibition of CPE at 1.6 μg/ml, but also significant proliferation of fibroblasts at slightly higher concentrations. Subsequent bioassay-guided fractionation led to the detection of gallic acid as a potentially active constituent that significantly reduced indirectly the CPE of EMCV on L929 cells in a dose-dependent manner. At 100 μg/ml, complete cytoprotection was noticed, without cytotoxic effects. Of the coumarins, umckalin showed the relatively strongest inhibitory effects in the range of 25 up to 50 μg/ml with 30% efficacy relative to the IFN standard.
Herbert Kolodziej, Albrecht F. Kiderlenb (2007), [16]	Gram-positive bacteria (Staphylococcus aureus, Streptococcus pneumoniae and β-hemolytic Streptococcus) Gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae) using the agar dilution method	Four Pelargonium root extracts: Methanolic, ethyl acetate, n-butanol and water	The crude methanolic Pelargonium root extracts were found to be moderately active against the tested bacteria with MICs of 5 7.5 mg/ml, the ethyl acetate, n-butanol and water phases exhibited fairly high antibacterial effects as evident from MICs of 0.6–1.2 mg/ml. No significant differences were found between P. sidoides and P. reniforme extracts regarding this particular biological activity.
Martin Michaelis, Hans Wilhelm Doerr, Jindrich Cinatl Jr. (2011), [19]	**Virus** / **Cell line** H1N1 / MDCK H3N3 / MDCK H5N1 / Vero RSV / Vero HCo-229E / Caco-2 Adeno 3 / Caco-2 Adeno 7 / Caco-2 Parainfluenza 3 / LLC-MK2 Coxsackie A9 / HFF Rhino 16 / Mel-Ho	Incubation with increasing concentrations of EPs® 7630	EPs® 7630 did not decrease viability of all investigated cell types in concentrations up to 100 g/ml. EPs® 7630 did not affect CPE formation induced by H5N1, adeno 3, adeno 7, or rhino 16 in the examined concentrations up to 100 μg/ml. EPs® 7630 interfered with CPE formation caused by H1N1, H3N2, RSV, HCo-229E, parainfluenza 3, or coxsackie A9 EPs® 7630 at a concentration of 100 μg/ml completely suppressed replication of H1N1, H3N2 and of RSV. Virus titers of coxsackie A9 were reduced by about 10,000-fold, of parainfluenza 3 by about 150-fold, and of HCo-229E by about 10 fold.
Hu K., Guan W., Bi W., Zhang W., Li L., Zhang B. (2020), [21]	284 patients with COVID-19: Lianhuaqingwen (LH) capsules group (142) and controls (142)	Experimental group: 4 LH capsules thrice daily for 14 days + conventional treatment based on the 4th version of *Protocol for Diagnosis and Treatment of Novel Coronarvirus Pneumonia.* Control group: Conventional treatment alone.	Treatment vs controls: recovery rate 91.5% vs. 82.4% (p = 0.022), lung improvement based on CT 83.8% vs. 64.1% (p < 0.001), clinical cure 78.9% vs. 66.2% (p = 0.017), symptoms alleviation 7 vs. 10 days, p < 0.001), time to recovery of fever (2 vs. 3 days) (p < 0.001), fatigue (3 vs. 6 days) (p < 0.001) and coughing (7 vs. 10 days) (p < 0.001). The rate of conversion to severe cases and viral assay findings were similar in both groups (both $p > 0.05$).
Duan C., Xia W.G., Zheng C.J., Sun G.B., Li Z.L., Li Q.L. (2020), [22]	123 COVID-19 patients; Treatment group (82); control group (41)	Treatment group: Jinhua Qinggan granules + conventional treatment (antibiotics, antiviral drugs	The hospitalization rate was significantly lower in the ginggan group in compare to the control group 10,98% vs 24,39% (p < 0.05).

(*continued on next page*)

Table 1 (*continued*)

Authors (year) [reference number]	Subjects	Intervention	results
		and mechanical ventilation); Control group: conventional treatment only	The ginggan group had lower incidence of fever 53,1% vs 80,3% ($p < 0.05$), coughing 42,9% vs 66,1% ($p < 0.05$) and fatigue 53,8% vs 77,6% ($p < 0.05$). Adverse effects ratio was higher in the experimental group than in the control group (32,93% vs 0%).

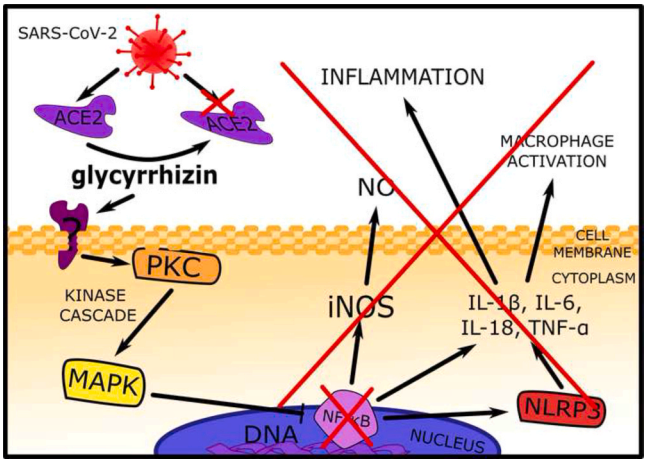

Fig. 1. Potential molecular pathway of glycyrrhizin in SARS-CoV-2 infection. ACE2 – angiotensin-converting enzyme 2; PKC – protein kinase C; MAPK – p38 mitogen-activated protein kinase; NF-κB – nuclear factor kappa B; NLRP3 – NOD-like receptor family, pyrin domain-containing protein 3 inflammasome; ILs – interleukins; TNF – tumor necrosis factor; iNOS – inducible NO synthase.

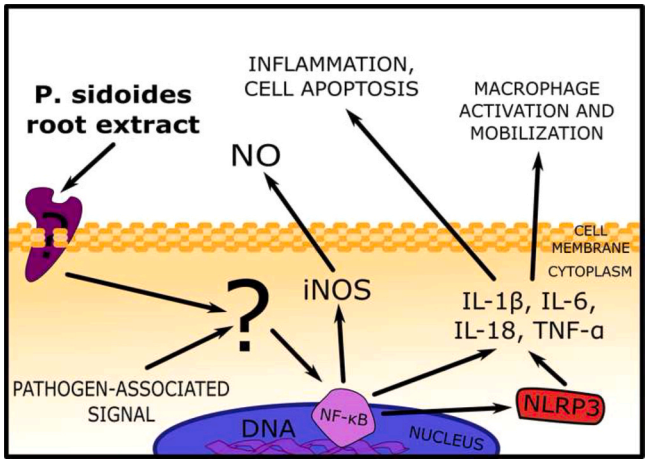

Fig. 2. Potential molecular pathway of P. sidoides root extract in SARS-CoV-2 infection. NF-κB – nuclear factor kappa B; NLRP3 – NOD-like receptor family, pyrin domain-containing protein 3 inflammasome; ILs – interleukins; TNF – tumor necrosis factor; iNOS – inducible NO synthase.

2.2.2. *Antiviral properties of Pelargonium sidoides root extract*

Although the exact pharmacodynamics of the P. sidoides root extract is unknown, scientists have been able to shed light on the antibacterial, antiparasitic and antiviral effects of African geraniums. Kolodziej et al. in their in vitro studies investigated the impact of P. sidoides root extract (EPs 7630) on macrophages [15,16]. Researchers revealed that Eps 7630 induces production of interferons, tumor necrosis factor (TNF), IL-1, IL-18 and nitric oxide (NO), what can be inter alia a result NLRP3 inflammasome activation [16]. Moreover, EPs 7630 tends to increase the activation and mobilization of macrophages. This study has some limitations, e.g. only murine macrophages were used and they were exposed to encephalomyocarditis virus not SARS-CoV-2 or even other type of coronavirus. However, this data indicate that the African geranium root extract may induce a non-specific immune response facilitating pathogen recognition and destruction in humans and further studies are needed to confirm this effects [15,16]. Interestingly, studies with Leishmania-infected RAW 264.7 cells showed that the expression of IL-1, IL-12, IL-18, TNF, IFN-α, IFN-γ and iNOS was minimal in non-infected cells and significant in infected cells [16]. This would indicate that EPs 7630 promotes not general but pathogen oriented upregulation of cytokines. Importantly, severe cases of COVID-19 are most often a result of excessive immunological response, therefore, further stimulation of e.g. NLRP3 can lead to deterioration of patients condition. However, NLRP3 mediated inflammation is more controlled one, as it leads rather to apoptosis, not necrosis what limits the release of various inductors of inflammation. Therefore, this inflammatory process is most likely more pathogen oriented and self-restraining, thus very beneficial for patients. Nevertheless, it appear that *P. sidoides* root extracts would be most effective at the early stage of COVID-19 and not in cases of excessive inflammatory response. This aspect needs further investigation in clinical studies. The possible molecular pathway of impact of glycyrrhizin on infected cells is shown in the Fig. 2, however, there are many unknowns in that process and it needs more studies to be fully comprehended.

A meta-analysis by Schapowal et al. showed a significant improvement in the well-being of patients with a common cold after using P. sidoides root extract (EPs 7630). Patients showed substantial reduction of symptoms after 5 and 10 days of treatment in compare to placebo, with a relative risk of: $RR_{(5)} = 1.73$ ($p < 0.05$), $RR_{(10)} = 1.06$ ($p < 0.05$). Moreover, relative risk of complete symptom remission was $RR = 2.52$ ($p < 0.05$), $RR = 2.13$ ($p < 0.05$), after 5 and 10 days respectively [17]. Similar results were obtained by Timmer and colleagues, and Kolodziej and Kiderlen showed inhibitory effects of EPs 7630 on bacterial growth in vitro, including tuberculosis or staphylococci [16,18]. The aforementioned promising results prompted Michaelis et al. to study the effect of EPs 7630 on the virulence and replication of viruses that most commonly cause upper respiratory tract infections [19]. Pelargonium sidoides root extract significantly reduced the number of viruses and their ability to penetrate into host cells. However, EPs 7630 affected only enveloped viruses, i.e. HCo-229E coronavirus, H1N1, H3N2, RSV, parainfluenza 3 and coxsackie A9 viruses. In the case of HCo-229E, the 50% virulence inhibition rate was achieved with concentration of 44.50 ± 15.84 μg/ml, and the therapeutic index (TI) > 2.3 (due to the low toxicity of EPs 7630, the researchers were unable to determine the toxic dose) [19]. Regarding results of this clinical and in vitro studies EPs 7630 is an effective antiviral agent.

2.2.3. *Pharmacokinetics*

The studies described above were performed on cell lines, which makes it difficult to determine the dosage of African geranium root extract, but 30 drops of aqueous solution or one 20 mg tablet daily was used in clinical studies, and its appear that it allowed to achieve effective plasma concentrations [17]. Sadly there are no researches describing P. sidoides pharmacokinetics.

2.2.4. *Pelargonium sidoides root extract as a potential COVID-19 treatment*

As it was mentioned before, the pharmacodynamics of Eps 7630 is

still not fully comprehended, although it is proven that it increases the activation and mobilization of macrophages and induces production of interferons, TNF, IL-1, IL-18 and nitric oxide (NO), particularly in infected cells. Moreover, P. sidoides root extract show antiviral properties in clinical and in vitro studies, inter alia against HCo-229E coronavirus [15–17]. Considering the high similarity of SARS-CoV-2 to other coronaviruses that also have one RNA strand and form a lipid envelope, it can be suspected that EPs 7630 will act on SARS-CoV-2 and reduce its virulence, however, due to the recent appearance of this virus, till this date still lacks hard scientific evidence for this hypothesis [20].

2.3. Herbs in combination with conventional therapy in COVID-19 treatment

There are many studies on combination of traditional Chinese medicine and western medicine. Unfortunately only few are randomized controlled trials.

One of these is a multicenter, prospective, randomized controlled trial investigating efficacy and safety of Lianhuaqingwen (LH) capsules (containing Radix et Rhizoma Glycyrrhizae, *Gancao*) [21]. Hu et al. enrolled into the study 284 symptomatic patients with COVID-19 (142 each in treatment and control group) and received conventional treatment alone (control group) or conventional treatment in combination with LH capsules, four capsules trice daily for 14 days (treatment group) [21]. The diagnosis and conventional treatment was based on the 4th version of *Protocol for Diagnosis and Treatment of Novel Coronarvirus Pneumonia.*

The recovery rate, the rate of improvement in chest computed tomographic manifestations and clinical cure in treatment group as compared with control group were 91.5% vs. 82.4% ($p = 0.022$), 83.8% vs. 64.1% ($p < 0.001$) and 78.9% vs. 66.2% ($p = 0.017$) respectively [21]. The median time to symptom recovery was markedly shorter in treatment group (median: 7 vs. 10 days, $p < 0.001$). Time to recovery of fever (2 vs. 3 days), fatigue (3 vs. 6 days) and coughing (7 vs. 10 days) was also significantly shorter in treatment group (all $p < 0.001$) [21]. The rate of conversion to severe cases and viral assay findings were similar in both groups (both $p > 0.05$) [21].

However, this study has some limitations, such as luck of blinding and no placebo group, what authors explained with the fact that placebo-controlled trial would be unethical and "because of the urgency of the outbreak that entailed a timely treatment" [21]. The duration of the study was very short, what is associated inter alia with the lack of mortality rates, therefore, a longer follow-up period would significantly increase relevance of the findings.

Another interesting study was performed by Duan et al. [22]. In this randomized trial researchers assessed the efficacy of Jinhua qinggan granules in COVID-19 pneumonia treatment (Glycyrrhizae Radix et Rhizoma) in combination with standard treatment [22]. 123 patients with COVID-19 were randomized to treatment group (Jinhua Qinggan granules plus conventional treatment: antibiotics, antiviral drugs and mechanical ventilation) – 82 and control group (conventional treatment only) – 41.

In compare to controls, patients in ginggan group had significantly lower incidence of fever 80,3% vs 53,1%, coughing 66,1% vs 42,9%, fatigue 77,6% vs 53,8%, with $p < 0,05$ for all parameters [22]. The treatment group score in the Hamilton anxiety scale was also lower in the treatment group. No predominance of combination treatment in recovery of body pain, headache, nausea and vomiting, runny nose, sore-throat, itching throat has been noted. Finally and most importantly, the hospitalization rate was significantly lower in the ginggan group in compare to the control group 10,98% vs 24,39% [22].

These results suggest Jinhua qinggan granules may relieve some of the COVID-19 pneumonia symptoms and improve psychological comfort of the patients. However, it is worth noting the adverse effects ratio was higher in the experimental group than in the control group (32,93% vs 0%) [22]. Therefore it can be assumed, that there have been some interactions between ginggan granules and other drugs, which were responsible for some, if not for majority, of reported adverse effects. The disadvantage of the trial is a short duration time (5 days), small group of patients and lack of mortality rates. Considering the time of disease duration, COVID-19 require a longer follow-up period.

According to WHO, there is no specific antiviral therapy for COVID-19, so new trials searching for effective anti-COVID-19 treatment (including TCMs) are still registering, such as study by Xiao et al. [23].

This perspective, open-labeled, randomized, controlled trial assess whether TCMs are safe and effective for treating COVID-19 infection. Estimated enrollment is 150, will be randomized in a 1:1 ratio. The experimental group will be treated with conventional medicines (oxygen therapy, antiviral therapy - alfa interferon via aerosol inhalation, and lopinavir/ritonavir) and TCMs granules for 14 days. The control group – only with conventional medicines (for 14 days). There is not specific information about kind of TCMs. The incidence rate of ARDS development, the time to fever resolution rate and to recovery of lung injury (chest radiographic evidence) and more will be measured. Currently, the trial is still recruiting and estimated primary completion date was January 22, 2021, however, there is still no data published.

3. Discussion

Herbal products for centuries were successfully used for treatment of various infections and are still used nowadays. Moreover, herbal products are getting more, and more popular in XXI century. Sadly, in many cases there is not enough scientific data to prove effectiveness of a particular herb or to delineate its pharmacodynamics, although preclinical studies are often promising, as it was described above. Among all herbal products and ingredients of TCM mixes Glycyrrhiza glabra and Pelargonium sidoides are best researched, and appear to be effective, however other plants or substances were also analyzed. Wang et al. investigated an antiviral effect of maxingshigan–Yinqiaosan a traditional TCM herbal mix composed of 12 herbs including Ephedra herb [24]. Maxingshigan–Yinqiaosan (200 ml four times daily) reduced the time to fever resolution among H1N1 infected patients by 37% (95% CI, 23–49%), oseltamivir (75 mg twice daily) by 34% (95% CI 20–46%), and oseltamivir plus maxingshigan–yinqiaosan by 47% (95% CI 35–56%). Therefore, maxingshigan–yinqiaosan could be used as a comedication with oseltamivir, as it increases its effectiveness and probably has an antiviral properties itself [24]. However, research by Tan et al. show that oseltamivir is not effective against SARS coronavirus [25]. Mantani et al. studied antiviral properties of catechin, which is a flavonoid abundant inter alia in Ephedra herb, which is commonly used in TCM [26]. Researchers discovered that in vitro catechin inhibits H1N1 virus replication in dosage dependant manner [24]. However, Cai et al. investigated pharmacokinetics of catechin contained in green tea leaves indicating its very low bioavailability, therefore it is unlikely to use it as an effective antiviral treatment, and results of study by Wang et al. could be an effect of a different active compound [27].

As it was described above, Glicyrrhiza glabra and Pelargonium sidoides have a potential to be effective in treatment of SARS-CoV-2 infection, opposite to many other investigated herbs. However, in spite of some herbal products may be not sufficient as a main, solitary compound of COVID-19 treatment, they may be successfully introduced as a complementary treatment. For this purpose jinhua qinggan granules and LH capsules may be used, as they, if added to a conventional therapy, reduce the recovery time of COVID-19 symptoms. Moreover, jinhua qinggan granules significantly reduces the hospitalization rate. Treatment of COVID-19 is a great burden for public health care, therefore, faster recovery, achieved by a proper complementary therapy is very important, as it will help to ease hospitals and outpatient clinics. Furthermore, severe COVID-19 cases are still problematic and hard to treat, thus herbal products used even as an experimental treatment may be very useful in clinical practice.

There is no evidence that other herbs or herbal mixes could have or

have not antiviral properties, especially in view of SARS-CoV-2. However, Li et al. registered a meta-analysis in which they will analyze and describe the role of traditional Chinese herbal medicine in treatment of COVID-19 [28]. This promising study will hopefully summarize clinical experience of health care professionals gathered during pandemic, which is of great value.

4. Conclusions

Among all herbal products Glicyrrhiza glabra and Pelargonium sidoides are broadly investigated herbs with confirmed antiviral properties in both clinical and in vitro studies. What is important both herbs reduced replication and cytopathogenicity of particular coronavirus strains, and considering its pharmacokinetics it is possible to achieve therapeutic plasma concentrations after oral administration. In compare to standard therapies, combinations of products based on Glycyrrhiza glabra with standard therapies significantly reduces the hospitalization rate and occurrence of symptoms such as fever, chills, cough etc. among patients with COVID-19. It appear that *P. sidoides* root extracts would be most effective at the early stage of COVID-19 and not in cases of excessive inflammatory response. Regarding other herbal products used in traditional medicine in most cases there is a lack of evidence of their effectiveness in treatment of COVID-19, whilst some are very unlikely to have a clinical value in spite of promising in vitro studies. For example it is hardly possible to achieve a therapeutic concentration of catechin due to its low bioavailability. In case of the maxingshigan–yinqiaosan, it very unlikely for it to help in treatment of COVID-19, as it only enhance the effectiveness of oseltamivir, which is futile against SARS coronaviruses. Nevertheless, some herbal mixes, such as lianhuaqingwen capsules and jinhua qinggan granules, appear to be useful as a complementary therapy in conventional COVID-19 treatment. These herbal mixes reduces hospitalization rates, time to symptoms recovery and improve patient psychological comfort. However, herbs may interact with other drugs significantly increasing the risk of adverse effects occurrence. Therefore, liquorice root extract and P. sidoides root extract can be potentially used in prevention and as a treatment of COVID-19, while lianhuaqingwen capsules and jinhua qinggan granules can be useful as a complementary therapy to conventional treatment.

CRediT authorship contribution statement

Aleksander Gajewski: Conceptualization, Writing – original draft, Methodology. **Anna Kośmider:** Writing – original draft, literature search. **Aleksandra Nowacka:** Writing – original draft, literature search. **Oskar Puk:** Writing – original draft. **Michał Wiciński:** Project administration, Validation.

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