

Treatment of Early-Stage Covid-19 With a Herbal Compound, Xagrotin

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Introduction:

In designing and manufacturing new drugs, two new and strong trends have emerged. Biotechnology has developed a new group of biological drugs, and offers a completely new approach to drug design. And there is a growing trend towards the use of herbal products in the treatment of diseases (Robert,2000). The use of medicinal plants for the treatment of diseases has been around for centuries, and is still considered a major treatment in many developed and developing countries (Sindambiwe,1999). Currently, most modern drugs are chemical. But at the same time, about 30% of pharmaceutical products are of plant origin (Robert,2000). New research has shown that some herbs are used in traditional medicine. They have antiviral effects. The extract of some plants has been described as an antiviral agent (Vanden,1986). In particular, the antiviral effects of several types of flavonoids (Hayashi,1992 & 1997), Anthraquinones and their derivatives have been studied (Andersen, 1991 & Sydiskis, 1991). Hypericin and Pseudohypericin Which have a significant effect on retroviruses. From plant species Hypericum are taken (Meruelo,1988). It has also been shown that entroquinones that inhibit polyphenolic or sulfonate bridges inhibit the reverse transcriptase enzyme (Schinazi, 1990). Treatment of viral infections with existing drugs for reasons such as drug resistance due to mutations in viruses. Some latent infections and recurrent infections sometimes fail. Therefore, there is a growing need to find new antiviral compounds (Field,1994). Research on medicinal plants and their compounds is a useful strategy in this regard (Vlietinck, 1991). In the present study, the effects of inhibiting the antiviral activity of a herbal drug consisting of several plant species on the clinical status of 35 positive corona patients were investigated.

Related studies

The coronavirus disease 2019 (COVID-19) pandemic has caused a worldwide outbreak of respiratory illness. This review aims to evaluate the effectiveness and adverse events of herbal medicines for the treatment of COVID-19. METHODS: Twelve databases were searched through 12 May 2020. Randomized controlled trials (RCTs) and quasi-RCTs

assessing the effects of herbal medicines for the treatment of COVID-19 were eligible. The study selection and data extraction were performed by two independent reviewers. The Cochrane risk of bias tool was used for the assessment of the risk of bias in all included RCTs. Mean differences (MDs), risk ratios (RRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, and the effect sizes of the studies were pooled. RESULTS: Seven RCTs with a total of 855 patients were included. All included trials compared the combined therapy of herbal medicine with Western medicine to Western medicine alone. The combined therapy significantly improved the total effective rate (RR 1.23, 95% CI 1.13 to 1.34, $p < 0.001$), cough symptom disappearance rate (RR 1.45, 95% CI 1.12 to 1.89, $p = 0.005$), and sputum production symptom disappearance rate (RR 1.73, 95% CI 1.19 to 2.50, $p = 0.004$). Beneficial effects of the combined therapy were also seen in TCM syndrome score of cough (MD -1.18, 95% CI -1.34 to -1.03, $p < 0.001$), fever (MD -0.62, 95% CI -0.79 to -0.45, $p < 0.001$), dry and sore throat (MD -0.83, 95% CI -1.45 to -0.20, $p = 0.009$), and fatigue (MD -0.60, 95% CI -1.04 to -0.17, $p = 0.007$). The overall risk of bias of the included studies was unclear. No serious adverse events were reported. CONCLUSION: Significant effects of the combined therapy of herbal medicine with Western medicine were found, and revealed the potential role of herbal medicine in treating COVID-19. More high-quality RCTs are needed to further validate the effectiveness and adverse events of herbal medicine in the treatment of COVID-19. (Ang, L., et al, 2020).

Coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is evolving across the world and new treatments are urgently needed as with vaccines to prevent the illness and stem the contagion. The virus affects not only the lungs but also other tissues, thus lending support to the idea that COVID-19 is a systemic disease. The current vaccine and treatment development strategies ought to consider such systems medicine perspectives rather than a narrower focus on the lung infection only. COVID-19 is associated with elevated levels of the inflammatory cytokines such as interleukin-6 (IL-6), IL-10, and interferon-gamma (IFN-gamma). Elevated levels of cytokines and the cytokine storm have been linked to

fatal disease. This suggests new therapeutic strategies through blocking the cytokine storm. IL-6 is one of the major cytokines associated with the cytokine storm. IL-6 is also known to display pleiotropic/diverse pathophysiological effects. We suggest the blockage of IL-6 signaling and its downstream mediators such as Janus kinases (JAKs), and signal transducer and activators of transcription (STATs) offer potential hope for the treatment of severe cases of COVID-19. Thus, repurposing of already approved IL-6-JAK-STAT signaling inhibitors as well as other anti-inflammatory drugs, including dexamethasone, is under development for severe COVID-19 cases. We conclude this expert review by highlighting the potential role of precision herbal medicines, for example, the Cannabis sativa, provided that omics technologies can be utilized to build a robust scientific evidence base on their clinical safety and efficacy. Precision herbal medicine buttressed by omics systems science would also help identify new molecular targets for drug discovery against COVID-19. (Dzobo, K., et al, 2021).

Coronavirus disease 2019 (COVID-19) is a novel, human-infecting beta-coronavirus enveloped, positive-sense single-stranded RNA viruses, similar to the severe acute respiratory syndrome (SARS) infection that emerged in November 2002. In traditional Chinese medicine (TCM), the epidemic disease concepts of "febrile epidemics" (wenyi) or "warm diseases" (wenbing) are based on geographic and cultural aspects, and Chinese herbal medicine (CHM) played an important role in the treatment of epidemic diseases. CHM was widely used to treat patients suffered with SARS almost two decades ago during outbreak of SARS, with proven safety and potential benefits. TCM has also been widely used to treat cancer patients for a long history and much of them associate with immunomodulatory activity and are used to treat coronavirus-related diseases. We propose the use of CHM treatment principles for clinical practice, based on four main stages of COVID-19 infection: early, intermediate, severe, and convalescence. We suggest corresponding decoctions that exhibit antiviral activity and anti-inflammatory effects in the early stage of infection; preventing the disease from progressing from an intermediate to severe stage of infection; restoring normal lung function and improving consciousness in the severe stage; and ameliorating pulmonary and vascular injury in

the convalescent stage. We summarize the pharmaceutical mechanisms of CHM for treating coronavirus via antiviral, anti-inflammatory and immunomodulatory effects. (Huang, S. T., et al, 2020).

Background: There is currently no effective treatment against coronavirus disease 2019 (COVID-19). The optimal selection of interventions targeting the virus is unknown. Therefore, evidence from randomized controlled trials (RCTs) to support specific treatment against COVID-19 is urgently needed. The use of Chinese herbal medicines (CHMs) might have a role in the treatment and symptomatic management of patients with COVID-19. It was aimed at providing an overview of the available evidence and ongoing trials concerning the effects of CHMs for the treatment of COVID-19. **Methods:** This is a narrative review of relevant studies. Searches were conducted to identify documents published till April 22, 2020. Electronic databases, evidence-based collections, websites of relevant organizations, and trial registries were consulted. **Results:** A total of 25 guidelines on the treatment of patients with COVID-19 were identified. Four guidelines provided recommendations on the use of CHMs; these guidelines were developed in China and South Korea and were based on the consensus of experts exclusively. The remaining 21 guidelines provided no guidance on CHMs. No finished RCTs of CHMs for the treatment of patients with COVID-19 was found. According to the evidence evaluated in this review, a Cochrane review of CHMs for severe acute respiratory syndrome and five uncontrolled observational studies of the effects of CHMs in patients with COVID-19, the effects of CHMs for COVID-19 are unknown. A total of 52 ongoing clinical trials of CHM interventions for the treatment of COVID-19 were found. These trials will be carried out mostly in China (n = 51). Forty (77%) of the ongoing trials will be randomized, whereas 12 (23%) have an unclear sequence generation procedure. Forty-seven trials (90%) will have a sample size <400 participants. **Conclusions:** To the authors' knowledge, only the Chinese and the South Korean guidelines recommend CHMs as a treatment option for patients with COVID-19. These guidelines base their recommendations on the consensus of experts. Clinical guidelines or health authorities from other countries do not provide advice on CHMs.

Due to the absence of RCT, there is currently no reliable evidence on the effects of any specific CHM intervention for the treatment of patients with COVID-19. A high number of clinical trials of different herbal products are being currently conducted in China. (Lopez-Alcalde, J., et al, 2020).

Coronavirus disease 2019(COVID-19) refers to the pneumonia caused by novel coronavirus(2019-nCoV) infection in 2019. It is highly infectious, with quick spreading and a wide range of impact. It has been broken out in many countries around the world and has become a public health emergency of international concern. Chinese medicine has a long history in treating plague, and viral disease is the clinical advantage in Chinese medicine. Under the premise that there is currently no specific drug treatment, Chinese medicine has achieved certain effects in the treatment of COVID-19, which has attracted much attention and has been upgraded to a national strategy. Regarding the treatment of COVID-19 with Chinese medicine, it is believed that in terms of the name of Chinese medicine, the modern connotation of "uniform of typhoid and febrile disease" should be re-recognized, and it is advisable to use drugs based on specific clinical prescriptions and indications. In terms of pathogenesis, the COVID-19 has the pathogenesis rules including from the mild to severe conditions, from the surface to the inside, from the excess syndrome to the deficiency syndrome. We should pay attention to the Taiyang syndrome damaged by wet disease in initial stage, Shaoyang syndrome complicated with Yangming syndrome in the middle stage, phlegm-heat obstructing lung in critical period, lung and spleen deficiency in the recovery stage. In terms of clinical treatment strategies, Dayuan Yin is recommended to induce sweat and disperse the stasis in early stage. Xiaochaihu Decoction and Maxing Shigan Decoction is used to relieve both exterior and interior symptoms in middle stage. In critical stage, Tingli Dazao Xiefei Decoction, Weijing Decoction, Xuanbai Chengqi Decoction, Xiaoxianxiong Decoction, and Sanzi Yangqin Decoction are considered to reduce phlegm and clear heat. We should pay attention to nourishing Qi and strengthening the spleen by Zhuye Shigao Decoction, Sha-shen Maidong Decoction, and LiuJunzi Decoction in the later recovery period. It shall be noted that, no matter in the

initial mild stage, the middle and critical stages, or in the later recovery stage, Chinese medicine plays an important role, including preventing mild to severe disease, shortening the fever time, improving cough symptoms, increasing blood oxygen saturation and reducing mortality. Many studies have shown that the classical herbal formulae can alleviate the cytokine storm, regulate the immune imbalance, and produce the potential effect of synergistic treatment for COVID-19 through multiple components, multiple targets, and multiple pathways. (Su, K. L. and X. J. Xiong, 2021).

Background: In January, national guidelines were developed and recommended for use throughout China to fight coronavirus disease 2019 (COVID-19). Chinese herbal medicine (CHM) was also included as part of the treatment plans at various stages of COVID-19. Methods: We conducted a pilot randomized, controlled trial in patients with severe COVID-19 in Wuhan, China. Eligible adult patients were randomly assigned in a 2:1 ratio to receive either CHM plus standard care or standard care alone for 7 days. The primary outcome was the change in the disease severity category of COVID-19 after treatment. Results: Between Jan 31, 2020, and Feb 19, 2020, 42 out of 100 screened patients were included in the trial: 28 in the CHM plus standard care group and 14 in the standard care alone group. Among 42 participants who were randomized (mean [SD] age 60.43 years [12.69 years]), 21 (21/42, 50%) were aged ≥ 65 years, 35 (35/42, 83%) were women, and 42 (42/42, 100%) had data available for the primary outcome. For the primary outcome, one patient from each group died during treatment; the odds of a shift toward death was lower in the CHM plus group than in the standard care alone group (common OR 0.59, 95% CI 0.148-2.352, $P = 0.454$). Three (two from the CHM plus group and one from the standard care alone group) patients progressed from severe to critical illness. After treatment, mild, moderate, and severe COVID-19 disease accounted for 17.86% (5/28) vs. 14.29% (2/28), 71.43% (20/28) vs. 64.29% (9/28), and 0% (0) vs. 7.14% (1/28) of the patients treated with CHM plus standard care vs. standard care alone. Conclusions: For the first time, the G-CHAMPS trial provided valuable information for the national guideline-based CHM treatment of hospitalized patients with severe COVID-19. The effects of CHM in COVID-19 may be clinically important and

warrant further consideration and studies. Clinical Trial Registration: <http://www.chictr.org.cn/index.aspx>. Uniqueidentifier: ChiCTR2000029418. (Ye, Y. A. and G. C. C. Group, 2020).

STUDY DESCRIPTION:

The study has retrospectively investigated outcome of patients with Covid-19 who have been tested positive for Covid-19 and immediately after that treated with a herbal-compound called Xagrotin. The outcome is compared to the outcome of patients in same situation who have treated with standard treatment for Covid-19, but not including Xagrotin. 361 patients included in the first group and 178 in the second group. We analyzed the effect of drug, and also investigated impact of different factors, for instance gender, age, duration of disease, smoking habits and concomitant diseases on the outcome. Adverse events were also registered.

Key word: Covid-19, Herbal Compound, Xagrotin

STUDY DESIGN

This is an interventional, multi-center, randomized study in adult patients with Covid-19 that was conducted for 5 months (June 2020 – December 2020). The present study was performed to treat the risks of coronavirus disease. This study consisted of two phases and in parallel. Informed consent was obtained from all patients. In this study, 539 adults with laboratory or clinically confirmed Covid-19 disease in an outpatient setting were enrolled and divided into two groups: the study group (n=361) treated with Xagrotin extract 2 grams three times a day, plus the standard of care for covid-19, and the control group (n=178) was treated with the standard of care for covid-19, respectively. Patients enrolled in the current study at approximately 20 cities.

Inclusion Criteria

All adult patients in an outpatient setting who were confirmed as coronavirus patients were eligible to be included in the study.

Exclusion Criteria

In this study, we excluded the patients with the following criteria; age under 18 years, patients with incomplete information regarding sex, age, duration of disease, any drug usage, symptoms, ...etc.

Safety endpoints

The herbal medicine Xagrotin is a combination of several local plants from the Zagros Mountains located in Kurdistan. In various studies, these plants have been studied individually for different pathological conditions. The side effects have been reported safe, but the results showed that it is somewhat capable of affecting CYP3A4. Therefore, Combined usage of Xagrotin with drug should be closely monitored. The level of LC50 $1844 \pm 2/34$ mg/kg was obtained. In this study, by examining the doses of these plants in previous studies, their safest dose was calculated. These safe dosages combined to formulate Xagrotin. Due to the unavailability of Covid-19 vaccination in Iran and the deadly outbreak of the virus, Xagrotin was made available to the local population along with this study.

OUTCOME MEASURES

This outcome e study has the following three main criteria.

Row	Outcome	Title	Time Frame	Description
1	Primary Outcome Measure:	Mortality	30 days	Survival at 30th day time point
2	Primary Outcome Measure:	Duration of disease	30 days	Number of days the patient has experienced the symptoms
3	Secondary Outcome Measure:	Hospitalization	30 days	Number of participants who have been hospitalized for Covid-19

Eligibility Criteria:

The participants in this study are of both sexes (male-female) and the target age is between 18-94 years.

- Inclusion Criteria: Age 18 or higher, Newly diagnosed (no longer than 10 days), PCR or clinically confirmed Covid-19
- Exclusion Criteria: Severe pulmonary disease, Severe cardiovascular disease, Severe hepatic disease, Severe renal disease,
- Diabetes mellitus type one, Metabolic acidosis, Oxygen saturation <70%, Pregnancy, Breast feeding, Concomitant treatment with anticoagulation drugs, Concomitant treatment with CYP3A4 medicines with narrow therapeutic window

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