Call for proposal for fighting against COVID-19 : prevent and mitigate the epidemic with the *Artemisia annua*

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March, 23rd 2020

Abstract

The peak of the COVID-19 epidemic in France is expected to occur in the coming days or weeks and the exposure of healthcare workers and law enforcement officers is increasing. Strengthening their prevention is essential. However, resources are very limited. Surgical masks are already in short supply. The *Artemisia annua* is an antiviral medicinal plant widely used in China as a treatment for SARS-CoV in 2003 and for COVID-19 today. Taken as a daily decoction by healthcare workers and law enforcement officers, it could be very effective in enhancing prevention. Administered to hospitalized patients as a complement to conventional treatment, it could also reduce the risk of failover to a critical condition. The NGO La Maison de l'Artemisia can make available immediately and free of charge the *Artemisia annua* for the healthcare staff of the intensive care units. Moreover, 10 tons of *Artemisia annua* would be enough to provide the most severely affected patients with daily decoctions and help to contain the epidemic in France and Europe. Currently, 1,000 tons of *Artemisia annua* can also be rapidly mobilized in Africa.

To confirm the virtues of such a treatment, a clinical study must nevertheless be carried out beforehand. There are important arguments in favour of the usefulness of this clinical study:

1. The anti-infectious properties of *Artemisia annua* have already been proven. The discovery of one of its main active ingredients, artemisinin, a molecule effective against malaria, won the Nobel Prize for Medicine to the Chinese scientist Youyou Tu in 2015. The anti-viral properties of *Artemisia annua* have also been proven against hepatitis B and C viruses, HSV-1, Epstein-Barr and especially SARS-CoV [1][9].
2. Chinese health authorities have just announced, in an article dated February 17, 2020 [2], that in 85% of the COVID-positive cases, they administered herbal mixtures as adjunctive therapy, including *Artemisia annua* (Qing Hao) for moderate pulmonary syndromes. These treatments have helped to contain the epidemic in China.
3. In 2004, the World Health Organization commissioned a study on SARS-CoV that compares several types of treatments. The results show that the administration of medicinal decoctions including *Artemisia annua* in addition to conventional treatments was often effective in alleviating symptoms[7].
4. In an emergency situation such as the COVID-19 outbreak, where conventional drugs take time to pass clinical trials, readily available herbal medicines and natural products with proven safety can save time as a first line of defence.

5. *Artemisia annua* is a non-toxic medicinal plant containing hundreds of constituents active on a wide range of infectious diseases. It is easily accessible, inexpensive, available in large quantities and without proven side effects.

We propose that the Army Health Service conducts an *in vivo* clinical study to validate the efficiency of a treatment with *Artemisia annua* against COVID-19 as a prevention or adjunct to conventional treatments. The modalities of such a study are proposed in the remainder of the document. This study would have the advantage of lasting only a few days and being inexpensive, but above all it would not present the risks and difficulties of studying a new conventional drug. Given the urgency of the situation, the speed of a clinical study conducted through the Military Health Service can be a major advantage. The major difficulty of such a study and the reason why little work has been carried out so far is that *Artemisia annua* is a plant, and moreover is not currently listed in the French pharmacopoeia. The Maison de l'Artemisia is nevertheless able to provide free of charge all the *Artemisia annua* necessary to carry out such a study.

1 Technical Description

1.1 Use of Traditional Chinese Medicine to treat COVID-19

During the SARS-CoV epidemic that occurred in late 2002 and spread to the Chinese province of Guangdong in 2003, Traditional Chinese Medicine (TCM) was widely used as a complement to conventional medicine. In response to the new SARS-CoV-2 (COVID-19) epidemic once again affecting the country, China turned again to TCM. It opted for a hybrid solution: in 85% of COVID-19 positive cases, complementary herbal treatment was provided to patients by Chinese hospitals to complement or replace conventional antivirals. The justification for this decision, which is without equivalent in the West, is supported by the numerous studies that have shown the benefits of TCM, both preventive and curative [2]. The decisions of the Chinese health authorities were also explained in an editorial published on 03/13/2020 in *Nature Plants* in which Chinese doctors recall the important role of complementary treatments in the regulation of the epidemic in China [3]. Each patient is treated with a mixture of about ten medicinal plants tailored to his symptoms. The Chinese government has sent to all its hospitals a list of the main combinations of complementary treatments in its Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia, Version 7. *Artemisia annua* plays a special role in this because it is used alone and not mixed with other plants. It is used to resolve symptoms of moderate respiratory difficulty. Today, these cases pose a problem for our health authorities as they are likely to worsen and occupy places in intensive care units as well as to mobilize artificial respirators. The *Artemisia annua* has the advantage of having no side effects and being non-toxic. It is also available in large quantities and is very inexpensive.

1.2 Proximity between SARS-CoV and COVID-19 and proven results of traditional Chinese medicine in SARS-CoV treatment

SARS-CoV and COVID-19 are both members of the coronavirus family. It is logical to focus today on the treatments used during the 2002 epidemic. Some SARS-CoV treatments such as chloroquine are now showing promising results against COVID-19. The effectiveness of chloroquine in eliminating the SARS-CoV virus was proven a few years ago [5]. Based on this result, it offers a serious avenue for research in the fight against COVID-19 [6]. The example of chloroquine shows that drawing on the therapeutic avenues already studied for SARS-CoV may prove to be a rapid short-term solution to deal with the COVID-19 pandemic emergency, despite the specificities of the two viruses.
However, treatments that combine conventional medicine and traditional Chinese medicine to fight SARS-CoV have already proven their effectiveness. In 2004, the World Health Organization commissioned a study on the complementarity between conventional treatment and traditional Chinese medicine in the treatment of SARS-CoV [7]. This study highlights that under certain conditions conventional treatment with antiviral drugs is more effective when accompanied by complementary

herbal treatment. According to the study, this synergy is all the more important for moderate to severe cases, which are those that pose a problem for health services today by mobilizing dedicated personnel, equipment and infrastructure over an unusually long period of time. Concretely, this treatment of traditional Chinese medicine takes the form of decoctions of a dozen medicinal plants. The formulation is adapted to each type of case and the *Artemisia annua* is used in cases of moderate to severe respiratory difficulties.

1.3 Antiviral properties of *Artemisia annua* and the potential of such a treatment for COVID-19

While TCM is unique in that it offers each patient a personalized treatment, the *Artemisia annua* has a special place. It is used to treat fevers and respiratory syndromes and its anti-viral virtues have now been demonstrated. For example, artemisinin, one of the active ingredients in *Artemisia annua*, known for its anti-malarial properties, also has significant antiviral activity against HSV-1, HSV-2, HBV and HCV. In particular, it has been shown *in vitro* that artemisinin inhibits the replication of hepatitis C virus, which is a single-stranded RNA virus, in the same way as COVID-19 [9][10][16]. After the SARS-CoV epidemic in 2003, the antiviral effects of more than 200 Chinese medicinal plants were studied *in vitro* by the team of Shi-You Li [12]. Among these, it was shown that *Artemisia annua* exhibited with *Lycoris radiata*, *Pyrrosia lingua* and *Lindera aggregata* significant *in vitro* inhibition of SARS-CoV (measured by MTS method [11]).
Very recent studies on COVID-19 also confirm the potential of *Artemisia annua* in the fight against the epidemic. A study still under revision dated 03/13/2020 attempts to numerically simulate the chemical inhibition of test molecules on the main protease of COVID-19 (PDB ID: 6LU7). Among the molecules with the greatest inhibition potential, four are among the active ingredients found in the *Artemisia annua*: luteolin, kaempferol, quercetin and apigenin [13][15]. These results echo another study that uses supercomputers to screen for molecules that could potentially prevent the virus from binding to ACE2 receptors, particularly in the lungs. The study concludes that the 3rd and 5th best candidates are luteolin and quercetin, both contained in the *Artemisia annua* [14]. These recent results support the use of *Artemisia annua* as an adjunct treatment to combat COVID-19.

1.4 Need for conducting a clinical study

A complementary treatment based on *Artemisia annua* would be a serious candidate in the fight against COVID-19. First and foremost, a clinical study should be conducted as soon as possible to prove the efficiency of such a treatment (complementary or not) and then provide it to healthcare workers and patients with severe symptoms. By conducting the clinical study in the next few days, it will be possible to draw sufficient conclusions and potentially improve the effectiveness of the treatments at the peak of the epidemic in a few days or weeks.

We propose that the military provides the missing link to validate the efficiency of a treatment based on *Artemisia annua*: an *in vivo* preclinical study. The modalities of such a study are proposed in the following section. This study would have the advantage of lasting only a few days (14 days for the complete study, but first results will be available after one week), being very inexpensive and allowing a decision to be made on the efficacy of such a treatment complement. Depending on the conclusions of this study, it will then be time to move to the next level to support the healthcare staff and improve the treatment of high-risk cases.

2 Project plan

2.1 Planning

See Appendix A

2.2 Estimated Costs

The cost of a comparative study for about 60 people is about €1,000 per patient. The *Artemisia annua* would be the main medication tested and would be provided free of charge through the association La Maison de l'Artemisia. This study would therefore cost about €60,000 to carry out.

Once the study is carried out, if it proves to be conclusive, it would involve buying and importing *Artemisia annua* at around 50 €/kg shipped to metropolitan France. With a standard 7-day treatment and a dosage of 10g per person per day, we obtain a treatment cost of around € 3.50/person. To preventively treat the entire French nursing staff, i.e. about 1 million people, we would have to pay about 3.5 million Euros. This corresponds to 70 tons of dry plants that are immediately available in Africa.

3 Justifications

3.1 Impact

As explained in the first part, such a clinical study would make it possible to provide a prevention solution as soon as possible and to assist the healthcare workers. Given the imminence of the contamination peak, it is vital to be very effective in the fight against COVID-19. *Artemisia annua* can therefore be an opportunity to preserve healthcare workers and law enforcement personnel in the coming weeks. It is also a potential solution to stabilize and decrease the severity of symptoms for the most severely affected patients. In the long term, it also opens up a new therapeutic avenue. The potential benefit of such a study is therefore gigantic in view of the low investment required to conduct these clinical trials. This is a possible treatment route for the disease. We cannot afford to miss such an opportunity.

3.2 Credibility

The *Artemisia annua* is a more than credible solution. It presents very conclusive results with TCM in China to treat respiratory syndromes of both SARS-CoV in 2002, and especially COVID-19 today. Moreover, its low cost and high availability ensure very rapid delivery in the event of successful clinical trials. Very recent studies on the antiviral properties of *Artemisia annua* suggest that this plant contains several active ingredients that prevent the virus from attaching to lung cells.

3.3 Calendar

The conduct of clinical trials is specified in Appendix A - Schedule. The deployment phase will depend on the results of the trials. In case of a favorable outcome, it will then be a matter of contacting all the hospitals in France to send the doses of *Artemisia annua* to the nursing staff as soon as possible. Between the hospital's approval and the reception of these doses, only 24 hours would be necessary due to the high availability of *Artemisia annua* and the investment of La Maison de l'Artemisia.

"Traditional Medicine, with its proven quality, safety and efficacy, contributes to achieving the goal of universal access to healthcare".

OMS, *Traditional Medecine Strategy*, 2014-2023

4 Appendix A: Controlled trial of the antiviral efficacy and safety of a decoction-based preparation of *Artemisia annua* for the treatment of COVID-19 (ARTCOV) patients

Open prospective study description	The *Artemisia annua* has been used for centuries in traditional Chinese medicine to treat fevers and other infections [19]. A growing number of studies shows that *A.annua* compounds also have *in vitro* and *in vivo* activity against immunological and viral diseases [21][20][18]. In particular, such as hydroxychloroquine [23], *Artemisia annua* and artemisinin derivatives have shown *in vitro* activity against SARS-CoV, a virus of the same family as COVID-19 [12]. We propose a study to evaluate the virological clearance of patients infected with SARS-CoV-2. This Phase II trial is designed as a prospective, open-label, controlled trial to determine the antiviral efficacy of *Artemisia annua* decoction preparation in COVID-19 patients.

Objectives	**Principal objective :**	Evaluate the duration of virological clearance for COVID-19 patients treated with *Artemisia annua* decoction preparation.
	Secondary objectives :	1. Assess the safety of *Artemisia annua* decoction-based treatment. 2. Assess symptom relief time. 3. Assess side effects and liver protein levels.

Criteria for studies	**Main criterion studied :**	Virological cure rate at day 6, defined as two negative qRT-PCR results on two consecutive days from pharyngeal-nasal swabs.
	Secondary criteria considered:	1. Incidence of serious and non-serious adverse events after initiation of therapy. 2. Time to resolution of symptoms associated with COVID-19. 3. Incidence of side effects such as vomiting, nausea, tremor. 4. Incidence of elevated liver protein ALT / AST levels .

Study population	Inpatient and outpatient male and female patients over 18 years of age with qRT-PCR confirmed SARS-CoV-2 infection with symptoms of upper respiratory tract infection managed in an inpatient or outpatient setting. To detect a difference in virologic clearance rate in the *Artemisia annua* arm compared to the control arm, a total of 60 patients is required (at a bilateral alpha of 5%, a power of 80% and a loss of 30% follow-up). The main exclusion criteria are patients with chronic cardiovascular and hepatic pathologies and pregnant women.	
Study phase	Phase II	
Study site	To be determined, multi-centric.	
Intervention	Oral administration :	
	Artemisia annua	1 L of decoction of *Artemisia annua* (10g) in 3 daily doses morning, noon, evening (1/3 - 1/3 - 1/3). Preparation of the decoction : 10 grams of *Artemisia annua* (dry leaves and stems) in 1 L of boiling water brought to a boil for 3 minutes [24].
Study procedures	**Day 0**	If selection criteria are met and informed consent is signed: clinical examination, vital signs, pharyngo-nasal swab, liver and kidney parameters, enumeration and blood count. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
	Day 1	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
	Day 2	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
	Day 3	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)

Day 4	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
Day 5	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
Day 6	Clinical examination, vital signs, pharyngo-nasal swab. Kidney and liver function parameters, enumeration and blood count and formula Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
Day 7	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
Day 8	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
Day 9	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
Day 10	Clinical examination, vital signs, pharyngo-nasal swab. Administration of treatment (*A.annua* up to two negative tests by qRT-PCR)
Day 14	Clinical examination, vital signs, pharyngo-nasal swab.

Study duration	Unspecified
Duration of participation	14 days

5 Appendix B : About La Maison de l'Artemisia

La Maison de l'Artemisia is a French humanitarian association (Law 1901) for the fight against malaria by the *Artemisia annua* and *afra* for the most vulnerable populations of the South. These two plants have been used in traditional medicine for centuries in China and East Africa respectively.

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