

Advocacy for the implementation of clinical trials of Artemisia herbal tea in the fight against Covid19 in Rwanda

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FR

Foreword

Antiviral herbal medicines have been used during many historical epidemics. This therapeutic approach is not an outdated practice. Thus, it has been used in the two previous coronavirus outbreaks - MERS-CoV in 2012, SARS-CoV in 2013 - or in recent seasonal epidemics caused by influenza and dengue viruses.

The review of the scientific literature shows that “extracts of *Lycoris radiata*, *Artemisia annua* and *Lindera aggregate*, as well as extracts of *Isatis indigotica*, *Torreya nucifera* and *Houttuynia cordata*, have shown anti-SARS effects”. Clinical trials have also shown that the plant flavone *baicaléine* can prevent or limit the entry of the dengue virus into the host and inhibit virus replication after it has entered the host. Additionally, natural products derived from the roots of *Pelargonium sidoides* and *Taraxacum officinale* (dandelion) have anti-influenza activities as they inhibit virus entry and key viral enzyme activities.¹

As a complementary treatment, herbal antiviral drugs can increase cure rates when combined with other treatments. Recent information reports that Chinese Health authorities announced in an article published in March 2020 that “for 90% of the Covid19 positive cases, they administered *Artemisia annua* (Qing Hao) as a complementary treatment for moderate pulmonary syndromes.²” This complementary treatment may have contributed to contain the epidemic in China.

In an emergency situation such as the current Covid19 pandemic, and in the absence of conventional treatment, the development of efficient synthetic drugs or possible vaccines is subject to the time frame of research and validation protocols through clinical trials.

Readily available herbal medicine and natural products with proven safety can save time and be used a first line of defence.

1 “Redeploying plant defences”, *Nature Plants* 6, 177 (2020).

2 Information from the French NGO *La Maison de l'Artemisia*.

In order to contribute to the reflection on the policies to be carried out to effectively combat the current pandemic, *Inter-Culturel* consultancy office, in close collaboration with doctors, researchers and specialists in these plants, has undertaken to gather the existing scientific information to make it available to the health authorities and to all the actors involved in the search for treatments and care protocols suitable for helping people who have contracted or are exposed to Covid19.

The file below brings together available research data on the antiviral properties and potential uses of *Artemisia annua* and *afra* in the context of the current health emergency.

Attached to this file is the document “Call for projects to combat Covid19: preventing and mitigating the epidemic with *Artemisia annua*”, written by the NGO *La Maison de l'Artemisia*, which offers a proposal for a clinical trial that could inspire health policy makers.

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Abstract

Artemisia species, particularly *Artemisia annua* (the annual wormwood) and *Artemisia afra* (the African wormwood) are well known for their antimalarial properties, which have been extensively studied and validated by clinical trials.

Their antiviral properties have been less studied, but the studies published to date are promising.

They open up a line of research that should be encouraged in the current race against time to find a cure for the Covid19 pandemic.

The scientific studies already carried out on Artemisia species show :

- the antiviral potential of the plant taken in the form of herbal tea or powder;
- the antiviral potential of some of its compounds: phytosterols, quercetin, luteolin, β -sitosterol, stigmasterol and tannins;
- the synergy of these compounds when the extract of the *totum* of the foliar parts of the plant is administered;
- the immunostimulatory potential of the plant;
- the efficacy of administering medicinal decoctions including *Artemisia annua* in addition to conventional treatments to alleviate symptoms;
- the absence of toxicity of the infusion or powder of the plant.

Considering on the one hand that cases, to date anecdotal but increasing in number, suggest that taking *Artemisia annua* herbal tea has had a curative effect on patients infected with Covid19 and that other cases tend to show that it would also have a preventive effect ;

considering, on the other hand, the current lack of available treatment for the deleterious effects of Covid19 ;

considering, finally, the availability of the resource in Rwanda, and the presence of researchers who have studied the plant and its properties ;

we believe that the conduct of clinical trials based on the taking of *Artemisia annua* and *afra* herbal tea should be very quickly encouraged, as the taking of *Artemisia annua* or *afra* herbal tea as a preventive measure, especially for particularly exposed persons such as health care personnel.

Research Review

Antiviral potential of *Artemisia annua* and *afra*

Several species of *Artemisia* have antiviral properties. This virus inhibitory activity was first described by Indian researchers in 1991 :

M.M. Abid Ali Khan, D.C. Jain, R.S. Bhakuni, Mohd. Zaim and R.S. Thakur

Occurrence of some antiviral sterols in *Artemisia annua*

Plant Science (Ireland) 75, 161-165., 1991

The research team evaluated the virus inhibitory activity of 21 plants against tobamovirus. Among the plant extracts tested, extracts of *Lawsonia alba*, *Artemisia annua* and *Cornus capitata* showed the highest virus inhibitory activity.

The authors comment on the results of their research as follows :

« Antiviral screening of higher plants has shown that some of them contain highly potent inhibitors of plant viruses which display varying degree of inhibition. This during our screening programme *A. annua*, *L. alba* and *C. capitata* plants were found to possess virus inhibitors.

Only a very few inhibitors have been fully characterized, and these show striking chemical variation. Some inhibitors were characterized as glycoproteins, protein and polypeptide in nature while other inhibitors showed the characteristics of carbohydrates or polysaccharides. Similarly the virus inhibition by strawberry and raspberry leaf extract was due to the presence of phenolic tannins and the inhibitor of *Begonia tuberhybrida* was identified as oxalic acid. In stone fruit plants e.g. *Prunus* sp. the inhibitor were of flavonoid in nature and related to quercitin .

Similarly the steroidal, triterpenoid glycosides and volatile constituents of plant origin have been shown to possess virus inhibitory activity. The range of their molecular weights varied greatly. However, the nature of a virus inhibitor present in *A. annua* was identified as a mixture of low molecular weight sterols which was further separated and identified as sitosterol and stigmasterol. Further the suggestion that these antiviral sterols affects hosts rather than viruses is supported by the fact that the number of lesions produced are reduced when the compound applied first followed by virus inoculation and evidence was found for reduction of lesion size viz. diameter of lesion. This is

the first report on sterols present in *A. annua* plant showing virus inhibitory activity. »

This research suggests that *Artemisia annua* antiviral agents are sterols, and that their virus-inhibiting effect is related to their protective action on virus hosts.

By comparing the antiviral effect of 7 species of *Artemisia*, a 2011 study showed that among the wormwood species evaluated, the effect of *Artemisia annua* was always the strongest and that the plant extract was often more potent than that of the synthetic antiviral *Acyclovir* against Herpes Simplex virus type 1 (HSV1) in vitro.

MK Karamodini, SA Emami, MS Ghannad, A Sahebcar.

Antiviral activities of aerial subsets of *Artemisia* species against Herpes Simplex virus type 1 (HSV1) in vitro

Asian Biomedicine vol 5-1, 2011, 63-6

After screening more than 200 Chinese medicinal plant extracts for their antiviral activity against the coronavirus associated with severe acute respiratory syndrome (SARS-CoV), extracts from 4 of these plants - *Lycoris radiata*, *Artemisia annua*, *Pyrrosia lingua* and *Lindera aggregata* - showed significant inhibition effects on the virus when SARS-CoV strain BJ001 was used for screening. The dose dependence of the antiviral activities has been determined by serial dilutions of the compounds. *Lycoris radiata* extract was the most potent. The second was *Artemisia annua* extract:

Shi-you Li, Cong Chen, Hai-qing Zhang, Hai-yan Guo, Hui Wang, Lin Wang a,b , Xiang Zhang c , Shi-neng Hua, Jun Yu, Pei-gen Xiao, Rong-song Li, Xuehai Tan,

Identification of natural compounds with antiviral activities against SARS-associated coronavirus

Antiviral Research 67 (2005) 18-23, © 2005 Elsevier B.V

Vincent Cheng & al (2007), also mention *Artemisia annua* as one of the promising antiviral and immunomodulatory agents tested against the SARS CoV in animals and in vitro:

Vincent C. C. Cheng, Susanna K. P. Lau, Patrick C. Y. Woo, et Kwok Yung Yuen

Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection

Clinical Microbiology Reviews, Oct. 2007, p. 660-694 Vol. 20, No. 4

Researchers from *Leiden University* provided in 2012 “a quantitative measure of the *in vitro* anti-HIV activity of *Artemisia annua* and *Artemisia afra*”:

« The objective of this study was to provide quantitative scientific evidence that the *Artemisia annua* tea infusion exhibits anti-HIV activity through *in vitro* studies. A second objective was to determine if artemisinin plays a direct or indirect (synergistic) role in any observed activity. This was done by the inclusion of a chemically closely related species, *Artemisia afra*, known not to contain any artemisinin in our studies.

Materials and methods: Validated cellular systems were used to test *Artemisia annua* tea samples for anti-HIV activity. Two independent tests with different formats (an infection format and a co-cultivation format) were used. Samples were also tested for cellular toxicity against the human cells used in the assays.

Results: The *Artemisia annua* tea infusion was found to be highly active with IC₅₀ values as low as 2.0 µg/mL. Moreover we found that artemisinin was inactive at 25 µg/mL and that a chemically related species *Artemisia afra* (not containing artemisinin) showed a similar level of activity. This indicates that the rôle of artemisinin, directly or indirectly (synergism), in the observed activity is rather limited. Additionally, no cellular toxicity was seen for the tea infusion at the highest concentrations tested.

Conclusion: This study provides the first *in vitro* evidence of anti-HIV activity of the *Artemisia annua* tea infusion. We also report for the first time on the anti-HIV activity of *Artemisia afra* although this was not an objective of this study. These results open the way to identify new active pharmaceutical ingredients in *Artemisia annua* and thereby potentially reduce the cost for the production of the important antimalarial compound artemisinin. »

Andrea Lubbe, Isabell Seibert, Thomas Klimkait, Frank van der Kooy.

Ethnopharmacology in overdrive: The remarkable anti-HIV activity of *Artemisia annua*

Journal of Ethnopharmacology (2012) JEP-7371

Antiviral active phytochemicals compounds of *Artemisias*

Sterols

A Chinese study, published in 2003, supports the discovery made a decade earlier of the antiviral potential of *Artemisia annua* sterols. According to the authors of the publication, sterols from *Artemisia annua*

have superior antiviral properties compared to other *Artemisia annua* molecules, such as artemisinin. The researchers also claim that *Artemisia annua* has greater antiviral activity than the other 20 medicinal plants tested :

Xiangjie Sun and Gary R. Whittaker.

Role for Influenza Virus Envelope Cholesterol in Virus Entry and Infection

Journal of Virologie. 2003 Dec; 77(23): 12543-12551

Artemisinin

While sterols have been identified as the most active antiviral agents in the plant, they are not the only active compounds that inhibit plant viruses.

A study published in 2008 shows that the bioactivity of artemisinin and its semi-synthetic derivative, artesunate, is not reduced to its antimalarial action but also includes the inhibition of certain viruses, such as human cytomegalovirus and other members of the herpesviridae family (e.g. herpes simplex virus type 1 and Epstein-Barr virus), hepatitis B virus, hepatitis C virus and bovine viral diarrhoea virus :

« Traditional Chinese medicine commands a unique position among all traditional medicines because of its 5000 years of history. Our own interest in natural products from traditional Chinese medicine was triggered in the 1990s, by artemisinin-type sesquiterpene lactones from Artemisia annua L. As demonstrated in recent years, this class of compounds has activity against malaria, cancer cells, and schistosomiasis. Interestingly, the bioactivity of artemisinin and its semisynthetic derivative artesunate is even broader and includes the inhibition of certain viruses, such as human cytomegalovirus and other members of the Herpesviridae family (e.g., herpes simplex virus type 1 and Epstein-Barr virus), hepatitis B virus, hepatitis C virus, and bovine viral diarrhea virus. Analysis of the complete profile of the pharmacological activities and molecular modes of action of artemisinin and artesunate and their performance in clinical trials will further elucidate the full antimicrobial potential of these versatile pharmacological tools from nature. »

Efferth T, Romero MR, Wolf DG, Stamminger T, Marin. JJG, Marschall M.

The antiviral activities of artemisinin and artesunate. Clin Infect Dis. 2008; 47:804-11

The antiviral potential of artemisinin contained in *Artemisia annua* has also been demonstrated by the following studies:

Romero Marta, Serrano Maria, Vallejo Marta, Efferth Thomas; Alvarez, Marcelino; Marin, Jose, **Antiviral Effect of Artemisinin from Artemisia annua against a Model Member of the Flaviviridae Family, the Bovine Viral Diarrhoea Virus (BVDV)**, *Planta Medica* 72(13):1169-74, November 2006

Marta R. Romero, Thomas Efferth, Maria A. Serrano, Beatriz Castaño, Rocio I.R. Macias, Oscar Briz, Jose J.G. Marin, **Effect of artemisinin/artesunate as inhibitors of hepatitis B virus production in an “in vitro” replicative system**, *Antiviral Research* 68 (2005) 75-83

Quercetin

Another active compound present in different *Artemisia* species, of which *Artemisa annua* and *afra*, is also identify to have antiviral action. This is quercetin, which has been shown to be a broad-spectrum antiviral.

This flavonoid is one of the active compounds in *Artemisia* :

J.F.S. Ferreira, Dave Luthria, Tomikazu Sasaki, Arne Heyerick
Flavonoids from Artemisia annua L. as Antioxidants and Their Potential Synergism with Artemisinin against Malaria and Cancer
Molecules 2010, 15, 3135-3170

Yang GE, Bao L, Zhang XQ, Wang Y, Li Q, Zhang WK, Ye WC
Studies on flavonoids and their antioxidant activities of Artemisia annua
Zhong Yao Cai. 2009 Nov; 32(11): 1683-6

James T. Mukindaa, James A. Sycea, David Fisher, Mervin Meyer
Effect of the Plant Matrix on the Uptake of Luteolin Derivatives-containing Artemisia afra Aqueous-extract in Caco-2 cells
Journal of Ethnopharmacology 130 (2010) 439-449

The antiviral property of quercetin has been identified as early as 1985:

Tej N. Kaul, Elliott Middleton, Jr., and Pearay L. Ogra
Antiviral Effect of Flavonoids on Human Viruses
Journal of Medical Virology 15:71-79 (1985)

A Chinese research team found that quercetin inhibits influenza A infection with a broad spectrum of strains. Mechanism studies showed that quercetin interacted with the HA2 subunit.

In addition, quercetin may inhibit the entry of H5N1 virus. This study indicates that quercetin, which has inhibitory activity in the early stage of influenza infection, also offers a therapeutic option for the development of effective, safe and affordable natural products for the treatment and prophylaxis of influenza A infections.

« Influenza A viruses (IAVs) cause seasonal pandemics and epidemics with high morbidity and mortality, which calls for effective anti-IAV agents. The glycoprotein hemagglutinin of influenza virus plays a crucial role in the initial stage of virus infection, making it a potential target for anti-influenza therapeutics development. Here we found that quercetin inhibited influenza infection with a wide spectrum of strains, including A/Puerto Rico/8/34 (H1N1), A/FM-1/47/1 (H1N1), and A/Aichi/2/68 (H3N2) with half maximal inhibitory concentration (IC₅₀) of 7.756 ± 1.097 , 6.225 ± 0.467 , and 2.738 ± 1.931 µg/mL, respectively. Mechanism studies identified that quercetin showed interaction with the HA2 subunit. Moreover, quercetin could inhibit the entry of the H5N1 virus using the pseudovirus-based drug screening system. This study indicates that quercetin showing inhibitory activity in the early stage of influenza infection provides a future therapeutic option to develop effective, safe and affordable natural products for the treatment and prophylaxis of IAV infections. »

Wenjiao Wu, Richan Li, Xianglian Li, Jian He, Shibo Jiang, Shuwen Liu, and Jie Yang
Quercetin as an Antiviral Agent Inhibits Influenza A Virus (IAV)
Viruses, Volume: 8, Issue: 1, pp. 6

The antiviral property of quercetin has also been demonstrated against the Dengue virus:

« Conclusion: Results from the study suggest that only quercetin demonstrated significant anti-DENV-2 inhibitory activities. Other bioflavonoids, including daidzein, naringin and hesperetin showed minimal to no significant inhibition of DENV-2 virus replication. These findings, together with those previously reported suggest that select group of bioflavonoids including quercetin and fisetin, exhibited significant inhibitory activities against dengue virus. This group of flavonoids, flavonol, could be investigated further to discover the common mechanisms of inhibition of dengue virus replication. »

Keivan Zandi, Boon-Teong Teoh, Sing-Sin Sam,
Pooi-Fong Wong, Mohd Rais Mustafa and Sazaly AbuBakar,
Antiviral activity of four types of bioflavonoid against dengue virus type-2a
Virology Journal 2011, 8:560

More recently, this bioflavonoid has been identified as a potential inhibitor of Covid19 in early March 2020.

«Therefore, nelfinavir and lopinavir may represent potential treatment options, and kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate appeared to have the best potential to act as COVID-19 Mpro inhibitors. However, further research is necessary to investigate their potential medicinal use.»

Siti Khaerunnisa, Hendra Kurniawan, Rizki Awaluddin,
Suhartati Suhartati, Soetjipto Soetjipto,
Potential Inhibitor of COVID-19 Main Protease (Mpro) from Several Medicinal Plant Compounds by Molecular Docking Studya

Preprints, 13 March 2020.

Furthermore, a team of researchers from the *Clinical Research Institute of Montreal* (IRCM), led by Dr. Michel Chrétien, has received an official invitation from China to supervise a clinical trial and, if successful, plan to add quercetin to the therapeutic arsenal to counteract the Covid19 epidemic.

Luteolin

Another antiviral flavonoid found in various species of *Artemisia* that have antimalarial properties is luteolin. This compound is particularly present in the species *Artemisia annua* and *Artemisia afra*.

This substance has, among others, anti-inflammatory, antituberculosis and antiviral properties.

Wenwen Dai, Jinpeng Bi, Fang Li, Shuai Wang, Xinyu Huang, Xiangyu Meng, Bo Sun, Deli Wang, Wei Kong, Chunlai Jiang and Weiheng Su
Antiviral Efficacy of Flavonoids against Enterovirus 71 Infection in Vitro and in Newborn Mice
Viruses, 2019

Like quercetin, luteolin has been identified as a potential inhibitor of Covid19:

Siti Khaerunnisa, Hendra Kurniawan, Rizki Awaluddin, Suhartati Suhartati, Soetjipto
Soetjipto,

Potential Inhibitor of COVID-19 Main Protease (Mpro) from Several Medicinal Plant Compounds by Molecular Docking Study

Preprints, 13 March 2020

It is worth noting that the intestinal absorption of luteolin from aqueous plant extracts is up to 5 times higher than for pure luteolin:

Zhou P, Li LP, Luo SQ, Jiang HD, Zeng S. **Intestinal absorption of luteolin from peanut hull extract is more efficient than that from individual pure luteolin.**,
Journal of Food Chemistry. 9-56, 2008, 296-300.

This fact has been confirmed in another research work conducted by JT. Mukinda et al. in 2010:

James T. Mukinda; James A. Syce; David Fisher; Mervin Meyer,
Effect of the plant matrix on the uptake of luteolin derivatives-containing Artemisia afra aqueous-extract in Caco-2 cells
Journal of Ethnopharmacology. 2010 Aug 9; 130(3): 439-49.

β-sitosterol and stigmasterol

The antiviral effect of β -sitosterol and stigmasterol of *Artemisia annua* is well known to the Chinese for 30 years :

Tan RV, Zheng WF, Tang HQ.
Biologically active substances from the genus Artemisia
Planta Med. 1998; 64:295-302.

However, according to researchers, this antiviral effect is not an inherent property of these molecules, but is attributed to the increased activity of the cell-mediated immune response that controls viral replication.

The use of a combination of β -sitosterol and β -sitosterol glucoside to treat HIV infection stabilizes CD4 cells in infected people and reduces IL-6. The antiviral properties of β -sitosterol and β -sitosterol glucoside have been

patented. The patent holders describe the effects in an article published in 1999 :

Bouic PJ, Lamprecht JH.

Plant sterols and sterolins: a review of their immune-modulating properties

Altern Med Rev. 1999 Jun;4(3):170-7.

Tannins

Proanthocyanidins, or condensed tannins, have mainly been studied for their antioxidant properties. *Artemisia afra* has a very high level of proanthocyanidins: 19,900 mg/100g :

Taofik O. Sunmonu, Anthony J. Afolayan

Evaluation of Polyphenolic Content and Antioxidant Activity of Artemisia Afra Jacq. Ex Willd. Aqueous Extract

Pakistan Journal of Nutrition 2012, 11, 520-525

In *Artemisia annua* the rate is lower but still important: 340 mg/100 g in the leaves of *Artemisia annua* and only 30 mg/100 g in the stems :

M Mazandarani et al.,

Essential Oil Composition, Total Phenol, Flavonoid, Anthocyanin and Antioxidant Activities in Different Parts of Artemisia annua L. in Two Localities (North of Iran)

Journal of Medicinal Plants and By-products (2012) 1: 13-21

A Chinese study tested the inhibitory effects of condensed tannins of *Artemisia annua* on herpes simplex virus type 2 and hepatitis B virus. Regarding the inhibition of herpes simplex virus type 2, the results showed that the condensed tannin of *Artemisia annua* was as effective as the conventional drug, *Acyclovir*.

With regard to hepatitis virus, the results showed that the condensed tannin of *Artemisia annua* exhibited mild cytotoxicity at 2.5 mg/mL and could significantly inhibit the secretion of HBeAg in the HepG2.2.1.5 cell line. The overall results of this research suggest that the condensed tannins of *Artemisia annua* have a high selectivity index against herpes simplex virus type 2 and hepatitis B virus :

Zhang JF , Tan J , Pu Q , et al.
A study on antiviral activity of Condensed Tannin of Artemisia annua.
Res Dev, Nat Prod 2004 ; 16 (4) : 307 - 11

Pierre Lutgen
Tannins in Artemisia: hidden treasure for prophylaxis
October 9, 2016

Plant toxicity

Artemisias have been used for thousands of years in China (*Artemisia annua*) and South Africa (*Artemisia afra*) and no toxic effects have been observed.

Concerning the contemporary period, the most convincing human trial on *Artemisia annua* plant toxicity comes from Uganda. This long-running experiment has been studied by the researcher Patrick Ogwang. In the *Wagagai* flower farm, more than 2000 workers have been drinking *Artemisia* tea every week since 2006. No negative effects were observed and malaria is no longer a problem for farm workers.

Professor Pamela Weathers of *Worcester Polytechnic Institute*, who has been studying *Artemisia annua* for several decades, says:

« In all our animal studies using mainly mice, but also rabbits and rats, we have never observed any toxicity of up to 100 mg of *Artemisia annua*-delivered artemisinin per kg animal body weight. Indeed, in several trials powdered *Artemisia* leaves were gavaged daily into mice for up to 9 and 14 days, respectively, with no adverse effects on any of the animals. »

Pierre Lutgen

No toxicity detected for *Artemisia annua* or *afra*
Review published online on August 5, 2019 on MalariaWorld.org

The lack of plant toxicity is demonstrated by numerous researches :

Meshnick., Jorge Ferreira & Jules Janick
Annual Wormwood (*Artemisia annua* L.)
International Journal for Parasitology. 2002 Volume: 32, Issue: 13, Pages: 1655-1660

Yang B, Zhou S, Li C, Wang Y
Toxicity and side effects of *artemisiae annuae*
Zhongguo Zhong Yao Za Zhi. 2010 Jan;35(2):204-7

Mbeh Ubana Eteng
Biochemical and Haematological Evaluation of Repeated Dose Exposure of Male Wistar Rats to an Ethanolic Extract of Artemisia annua
Phytotherapy Research. 2013, 04 2

Mukinda JT, Syce JA.
Acute and chronic toxicity of the aqueous extract of Artemisia afra in rodents
Journal of Ethnopharmacology. volume 112, issue 1 (2007) 138-44

G.A. Chuiwet
Etude préliminaire à l'utilisation d'une phytothérapie d'Artemisia annua à l'usage d'enfants < 5 ans
Thèse de doctorat en pharmacie, Université des Montagnes, 2011

Idris Ahmed Issa and Mohammed Hussien Bule
Hypoglycemic Effect of Aqueous and Methanolic Extract of Artemisia afra on Alloxan Induced Diabetic Swiss Albino Mice.
Evidence-Based Complementary and Alternative Medicine Volume 2015 (2015)

Many studies have shown that *Artemisia annua* is not only free of toxicity over a wide dosing gradient, but also stimulates the immune system. This effect is attributed to constituents other than artemisinin: essential oils, flavonoids, coumarins, polysaccharides, saponins, tannins, pentacyclic triterpenes. A research from *Université des Montagnes* in Cameroon even indicates that *Artemisia annua* tea lowers alanine aminotransferase and could be hepatoprotective :

Nkuitchou - Chougouo K. Rosien D., Kouamouo Jonas, Titilayo O. Johnson, Djeungoue P. Marie-Ange, Chuisseu Pascal, Jaryum, Kouemeni Lysette, Lutgen Pierre, Tane Pierre, Moudipa F. Paul

Comparative study of Hepatoprotective and Antioxidant Activities of Artesunate and Artemisia annua Flavonoids on rats hepatocytes
Pharmacognosy conference Sao Paolo, Aug 29-30, 2016

Only one isolated case of liver toxicity has been identified in the scientific literature, when other studies suggest that the plant generally has an hepatoprotective effect :

Francisco J. Ruperti-Repilado, Simon Haefliger, Sophia Rehm, Markus Zweier, Katharina M. Rentsch, Johannes Blum, Alexander Jetter, Markus Heim, Anne Leuppi-Taegtmeier, Luigi Terracciano &Christine Bernsmeier

Danger of Herbal Tea: A Case of Acute Cholestatic Hepatitis Due to Artemisia annua Tea
Frontiers in Medicine, 1 October 2019, Volume 6; Article 221

Note on the search for plant-based treatments

In the context of the current health emergency and the lack of efficient treatment solution for patients affected by Covid19 and in view of the fatal risks for some of the patients, conventional research protocols are proving inadequate.

Indeed, the process leading to the validation of a synthetic drug is very long and, while it may be relevant in normal times, is proving to be inadequate in times of pandemic and generalized crisis.

The journal, *Nature Plants* has clearly posed the dilemma of finding therapeutic solutions in times of health crisis. Here is a large excerpt from its March 2020 editorial:

« The complicated secondary metabolism of plants has been the source of countless medicinal compounds and leads for drug discovery. It is little surprise then that plant products and their analogues have been employed as an early line of defence against COVID-19. On 17 February, the Chinese State Council announced that chloroquine phosphate — a structural analogue of quinine, originally extracted from the bark of cinchona trees — can be used for treating COVID-19 patients. This anti-malarial also has broad-spectrum antiviral activity and regulatory effects on the immune system. Clinical evaluation of chloroquine phosphate in more than ten hospitals across several provinces in China has shown that it alleviates the symptoms for most patients and expedites virus seroconversion.

The epidemiologist Nanshan Zhong, who is credited with discovering the SARS coronavirus in 2003 and is advising on the management of the COVID-19 outbreak, has said that chloroquine phosphate is not a highly effective cure but its effects deserve attention, even though its pharmaceutical mechanism remains unclear. However, quinine and quinine derivatives have been used for two hundred years, and the bark from which it is extracted for far longer. Their safe usage and potential side effects are well established.

(...)

The rich tradition of herbal medicine in China is also being deployed against COVID-19.

In the newest version of the diagnosis and treatment plan issued by the National Health of Commission of China, traditional Chinese medicine decoctions are explicitly recommended.

Several patent herbal drugs, such as Huoxiang Zhengqi capsules, Lianhua Qingwen capsules and Radix isatidis granula, are being proposed as treatments, the latter two having also been used during the SARS-CoV outbreak in 2003.

Compared to chemical drugs, herbal medicines and plant natural products are less understood mechanistically, but several clinical investigations have been started to more precisely evaluate their effects.

(...)

In routine drug development, researchers first discover a drug molecule with potential therapeutic activity against a certain target, then optimize its structure and validate its function using in vitro experiments followed by animal and clinical trials.

By contrast, many herbal drugs have been used in clinics for hundreds or thousands of years, and thus their safety and effects have been repeatedly tested; chloroquine phosphate has been used to treat malaria for over 70 years.

Timeliness is another advantage, particularly during emergencies. Once a herbal decoction or component is found to be effective, it can be immediately used for treating patients, its safety already established. »

Redeploying plant defences

Nat. Plants 6, 177 (2020).

Conclusion

Considering on the one hand all researches carried out on *Artemisia annua* antiviral properties, these isolated compounds, and their potential synergy when the leaves and stems of the plant are administered in infusion or powder form, and considering, on the other hand, the lack of toxicity of the plant, the conditions are fulfilled to carry out clinical trials in the current health emergency context created by the worldwide diffusion of Covid19.

The writing of this review of the scientific literature by *Inter-Culturel* office team was concomitant with exchanges with the French NGO *La Maison de l'Artemisia*, which drew up a proposal for a clinical trial protocol presented in the document "*Call for projects to combat COVID19 : preventing and mitigating the epidemic with Artemisia annua*": "*Randomized controlled trial on the antiviral efficacy and safety of a decoction-based preparation of Artemisia annua for the treatment of COVID-19 patients (ARTCOV)*".

If the Rwandan health authorities deemed it appropriate, such clinical trials could be launched very quickly due to the availability of *Artemisia annua* in Rwanda. A precise location of *Artemisia annua* stocks available in Rwanda should then be carried out quickly in order to be able to send as soon as possible the necessary quantities for this trial to researchers and to the people who are the most at risk (health care workers, garbage collectors, food stores cashiers, public transport drivers, police and security forces...).

Indeed, Rwanda has not yet reached its peak of Covid19 contamination and it is necessary, in order to extend the efforts of the Rwandan Government, to do everything possible to test all possible clinical options before reaching it.

As recalled in the "*Call for projects to combat Covid19*" launched by NGO *La Maison de l'Artemisia*: "*the potential benefit of such a study is therefore gigantic in view of the low investment required to carry out these clinical trials. This is a possible treatment route for the disease. We cannot afford to miss such an opportunity.*"

Note on the traditional uses of Artemisia annua & Artemisia afra

The traditional medicinal use of a plant is considered to be established if documentary evidences can be gathered that a substance has been used for at least three generations for a specific health-related or medicinal use.

This information is important because in this case, the WHO considers that pre-clinical toxicity testing is not necessary, as traditional use and the lack of toxicity claims is considered to be evidence of the safety of the plant in accordance with medicinal practices. Preclinical toxicity testing is only required for new herbal medicinal products with no history of traditional use.

Artemisia annua traditional uses

Of Chinese origin, *Artemisia annua* has been part of the pharmacopoeia in this part of the world for at least 2000 years, particularly for the treatment of malaria:

Geldre EV, Pauw ID, Inze D, Montagu MV, Eeckhout EV (2000)

Cloning and molecular analysis of two new sesquiterpene cyclases from Artemisia annua L.

Plant Sci 158:163-171

Meier zu Biesen C (2010)

The rise to prominence of Artemisia annua L. The transformation of a Chinese plant to a global pharmaceutical.

Afr Sociol Rev 14(2):24-46

A compendium of Chinese plant usage entitled "*Fifty-two Prescriptions*", dating from 168 BC, mentions *Artemisia annua* (Qing Hao) as a medicinal herb.

The Chinese treatise on *materia medica* "*Shennong ben cao jing*", dating from the first century AD, and quoted in later works, documents the use of *Artemisia annua* as a food preservative, a remedy against summer heat

and for the treatment of 'intermittent fevers', a typical symptom of malaria fevers.

The "*Manual of Prescriptions for Emergency Treatment*" (Zhouhou Beiji Fang), dating from the fourth century AD, also describes a number of traditional medicinal preparations using *Artemisia annua*:

Willcox M (2009)

Artemisia species: from traditional medicines to modern antimalarials and back again.

J Altern Complement Med 15(2):101-109

The Pharmacopoeia of People's Republic of China also describes its use in the treatment of tuberculosis and jaundice:

WHO Library cataloguing-in-publication data (2006)

WHO monograph on good agricultural and collection practices (GACP) for Artemisia annua L.

World Health Organization (ISBN 924 1594438)

www.who.int/medicines/publications/traditional/Artemisia_Monograph.pdf

Castilho PC, Gouveia SC, Rodrigues AI (2008)

Quantification of artemisinin in Artemisia annua extracts by 1H-NMR.

Phytochem Anal 9(4):329-334

Liu H. et al. mention the traditional use of *Artemisia annua* for wound healing in China :

Liu H, Tian X, Zhang Y, Wang C, Jiang H (2013)

The discovery of Artemisia annua L. in the Shengjindian cemetery, Xinjiang, China and its implications for early uses of traditional Chinese herbal medicine qinghao.

J Ethnopharmacol 146(1):278-286.

Artemisia annua is also traditionally used in Iran as a medicinal plant for infants, as an antispasmodic, carminative or sedative:

Emadi (2013)

Phytochemistry of Artemisia annua.

http://edd.behdasht.gov.ir/uploads/178_340_emadi.pdf

Sharma G, Shankar V, Agrawal V (2011)

An efficient micropropagation protocol of an elite clone EC-353508 of Artemisia annua L., an important antimalarial plant.

Int. J Pharma and Bio Sci 2(4):205-214

The *Artemisia annua* decoction has also been used as an antihemorrhagic to treat diarrhoea:

Mirdeilami SZ, Barani H, Mazandarani M, Heshmati GA (2011).

Ethnopharmacological survey of medicinal plant in maraveh tappeh region, north of Iran.

Iranian J Plant Physiol 2:1.

http://www.iau-saveh.ac.ir/Files/Journal/2012-05-30_07.05.18_6.pdf

The effects of *Artemisia annua* on hemostasis are also well known in traditional Persian medicine:

Wang B, Sui J, Yu Z, Zhu L (2011)

Screening the hemostatic active fraction of *Artemisia annua* L. In-vitro

Iranian J Pharmaceutic Res 10(1):57-62

The table below lists the medicinal uses of different parts of the *Artemisia annua* L. plant:

Medicinal uses	Plant parts used
Anti-hemorrhagic	Whole plant
Diarrhea	Whole plant
Anemia	Stem
Nausea due to wet heat	Root
Intense fever	Rhizome
Malaria	Stem and leaves
Asthma	Leaves
Eye infections	Leaves
Bronchitis and sore throat	Leaves

Cholera	Leaves
Dengue fever	Leaves
Lupus erythematosus	Whole plant
Athlete's foot and eczema	Leaves
Chagas disease	Leaves
Schistosomiasis	Leaves
Viral hepatitis B	Leaves
Chills and fever	Whole plant
Skin disease	Leaves
Parasitic disease including schistosomiasis and leishmaniasis	Leaves

Reference : Alia Sadiq, Muhammad Qasim Hayat and Muhammad Ashraf, « Ethnopharmacology of *Artemisia annua* L.: A Review », in *Artemisia annua - Pharmacology and Biotechnology*, p. 16, Tariq Aftab · Jorge F.S. Ferreira, M. Masroor A. Khan · M. Naeem Editors, Springer-Verlag Berlin Heidelberg 2014

Among the uses quoted in the above table, we can highlight the treatment of pathologies of infectious and parasitic origin: Chagas disease, Malaria, Schistosomiasis, Leishmaniasis, but also of viral origin: Bronchitis, Hepatitis B and Dengue.

Artemisia afra traditional uses

Artemisia afra is one of the oldest African medicinal plants recorded by ethnobotanical studies and remains one of the most renowned and used

plants in South Africa. It also has medicinal uses throughout its natural range, which covers much of East Africa.

The list of its traditional uses covers a wide range of ailments.

N.Q. Liu et al. describe the traditional uses of the plant as follows:

Artemisia afra « is usually employed for treating a variety of ailments such as coughs, colds, headaches, chills, dyspepsia, loss of appetite, gastric derangement, colic, croup, whooping-cough, gout, asthma, malaria, diabetes, bladder and kidney disorders, influenza, convulsions, fever, heart inflammation, rheumatism and is also used as a purgative (Watt and Breyer-Brandwijk, 1932; Thring and Weitz, 2006).

These uses indicate that *A. afra* possesses antiviral, anti-bacterial and anti-inflammatory activities. Many different preparations of this plant are employed to treat the various symptoms and ailments. A syrup prepared from *A. afra* is used for bronchial troubles, while infusions or decoctions can be applied as a lotion to bathe hemorrhoids and for earache.

An infusion of leaves or roots of this species is also used for the treatment of diabetes in the Eastern Cape Province of South Africa (Erasto et al., 2005; Mahop and Mayet, 2007). Respiratory infections are treated through inhaling the vapor from boiling leaves and this vapor is also used to treat menstrual chill. Fresh tips are inserted into the nose for colds and headaches and into hollow teeth to treat toothache. The poultice of the leaves can be applied to relieve neuralgia, to treat the swellings in mumps and is placed on the abdomen to treat infantile colic.

It is also helpful to reduce colic by administering a tincture made of the leaves wetted by brandy (Watt and Breyer-Brandwijk, 1932). *Artemisia afra* is also used as an infusion. Usually, a quarter cup of fresh leaves is added to a cup of boiling water and the infusion is allowed to draw for 10 min. The mixture is then strained and the resulting infusion is sweetened with honey. This preparation is taken orally for relief of most of the above-mentioned ailments (Roberts, 1990).

The use of other medicinal plants or substances in combination with *A. afra* is also documented in African ethnopharmacology. In South Africa, preparations of *A. Afra* are often made in combination with brandy, sugar, ginger, thyme, rosemary, mint, chamomile, *Osmitopsis asteriscoides* or *Eucalyptus globulus*. A combination of *A. afra* and *E. globulus* is employed to treat influenza, and the infusion of the leaves and stems of *Lippia asperifolia* and *A. afra* is used as a formula for fevers, influenza, measles, and as a prophylactic against lung inflammations (Watt and Breyer-Brandwijk, 1932).

Decoctions of the leaves of *A. afra* and *Agrimonia bracteata* are used for colds in southern Africa while decoctions of *Tetradenia riparia* and umhlonyane

(Xhosa name for *A. afra*) with salt are used to treat coughs in the Transkei region of the Eastern Cape Province of South Africa (Hutchings et al., 1996).»

N.Q. Liu F. Van der Kooy R. Verpoorte

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About Inter-Culturel

Inter-Culturel is a private and independent Rwandan consultancy firm.

It has initiated a study and reflection group on care practices, research in phytotherapy, the links between conventional and traditional medicines and the recognition and structuration of the profession of traditional practitioner.

Within the framework of its activities, the *Inter-Culturel* research department supports advocacy and lobbying actions.

It is within this framework that the present document has been produced, in collaboration with NGOs, researchers and doctors.

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