

Research Article

On the pros and cons of utilizing crude herbal preparations as opposed to purified active ingredients, with emphasis on the COVID pandemic

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It is well recognized that many plants contain substances with pharmacological activities, and there is a large body of traditional knowledge regarding their use in different clinical situations. Yet, most physicians in the Western world are reluctant to use herbal preparations, mostly because there are no large-scale randomized controlled trials to support their application. In this Opinion Paper, which is not intended to be a comprehensive review of herbal or traditional medicine, we challenge this approach and propose that herbal treatments should be added to our armamentarium, even if cautiously. This pertains particularly to situations in which there are no existing well-studied, safe, and effective evidence-based approaches; the known pharmacological properties of the plant or plants being used are relevant to the pathophysiology of the disease and the safety profile of the herbal preparation is well established. Specifically, due to our own experience, we focus on the treatment of patients with COVID with the plant *Artemisia*, based on *in vitro* studies and small clinical trials, as an example of the approach we propose.

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It is well recognized that many plants contain substances that have pharmacological activities^{[1][2]}. For thousands of years, crude preparations and extracts of those plants were used as treatments for human diseases. There are numerous examples of plant-based treatments in ancient Western medicine and in traditional Chinese medicine^{[3][4]}. Some of these are being further studied and used as complementary treatments to this day^[5]. In contrast to this traditional approach, Modern Medicine is based on the concept that pharmacological treatments should be precise. Accordingly, medications are manufactured in a reproducible manner and contain one or at most a small number of purified active ingredients, of which the concentration is known and clearly written on the package. The optimal dosing of each medication is found in well-designed clinical trials. Using a crude herbal preparation that contains numerous pharmacological compounds, some of which we know very little about, is not compatible with this concept. Furthermore, when crude herbal preparations are employed, the concentrations of the pharmacologically active ingredients may vary from one plant to the other and may depend on numerous environmental factors. These could include, for example, the soil in which a plant was grown, the amount of water it has received, etc.^{[6][7]}

Although there are many levels of evidence, including case series, small trials, and even case reports and *in vitro* studies, evidence-based medicine (EBM) has become synonymous with large-scale randomized controlled trials (RCTs). While the significant advantages of RCTs are obvious, is the precision-based foundation of Modern Medicine truly feasible, given that biological systems like the human body are far from being precise? Can our adoption of precise dosing of a given medication

guarantee that we provide each patient with an optimal dose? We know from our practice that this is often not the case. First, a given medication may have numerous possible interactions with other medications, as well as with food and supplements^[8]. Second, the metabolism of drugs may vary between different patients^[9]. These factors are rarely being taken into account in RCTs. It is generally assumed that the maximal dose that has been tolerated in a clinical trial is suitable for all patients. Yet, often times more is not better^{[10],[10][11][12]}. It should also be taken into account that even if a specific medicine was tested by an RCT, this does not necessarily mean that it is safe and effective for a given patient. Moreover, the concept of using pure pharmacologically active substances does not take into account the complexity of the human organism, as opposed to the more holistic approach of traditional medicine^[13]. Importantly, while most herbal preparations have not been tested in large-scale RCTs, their safety has been assessed for hundreds of years^[5]. Indeed, many medicinal plants are readily available and may be common constituents in multiple kitchens and gardens^[14]. Another benefit of using plants, as opposed to medications is that they do not contain excipients, which were thought to be inert substances and have become a significant cause of adverse reactions^[15].

Under which clinical situation is there a place for using herbs and other natural substances? Clearly, in the case of a life-threatening disease, for which there is a proven and well-established treatment approach, we should always prefer using that treatment. However, when faced with a patient with an indolent disease, which does not yet require treatment, it is conceivable to attempt complementary therapy with an appropriate herbal preparation, based on the mode of action of its active ingredients^{[16][17]} (curcumin, harefa), rather than taking the “wait and see” approach. In addition, in the case of a refractory disease, one might try an experimental treatment (if available) or use an herbal preparation as part of the supportive care^[18]. This may also apply to a new disease that lacks a known treatment.

A good example of the latter situation is a pandemic caused by a novel virus, such as SARS-CoV-2. Initially, there had been no evidence-based treatment approach for this novel and potentially severe disease. This allowed the acceptance of low-level evidence, such as the small (54 patients) compassionate-use non-randomized trial of remdesivir in hospitalized patients^[19], which led to its widespread use, despite a problematic safety profile. It has also been realized quite early in the COVID pandemic that the rather insidious onset of the disease in most patients created a possible window of opportunity to intervene at home when the patients still had minimal symptoms^[20]. Physicians around the world attempted to use repurposed drugs, food supplements and other interventions in various combinations as the means to alter the course of the disease^{[21][22][23]}. Interestingly, while most physicians in the Western world were reluctant to use traditional medicine, it was widely accepted in Asia and Africa. Indeed, traditional Chinese medicine has been used successfully and has been shown to be safe and effective in small-scale RCTs conducted in China^{[24][25]}. Furthermore, many people in the Western world used food supplements and herbal treatments on their own, without any medical guidance^{[26][27]}. In fact, the NIH, realizing the need of the public for some guidance on possible treatments in the early stages of the disease, created a list of such food supplements, with their safety profile and the limited evidence available on their efficacy, though a disclaimer was added regarding the lack of sufficient support for or against their use¹.

In this paper, we focus on the plant *Artemisia*, which is an example of a highly studied plant with multiple well-established pharmacological activities, used mostly in developing countries. The genus *Artemisia* is one of the largest and most widely distributed genera of the family Asteraceae (Compositae). It is a heterogenous genus, consisting of over 500 diverse species distributed mainly in the temperate zones of Europe, Asia, and North America. Its different species have been used in

traditional medicine world-wide for many years^[28]. All *Artemisia* species contain pharmacologically active substances such as terpenoids, flavonoids, coumarins, caffeoylquinic acid, sterols, and acetylenes^{[29][30]}. Numerous *in vitro* studies, as well as small-scale clinical trials, have shown the activity of different *Artemisia* species in infectious, malignant, respiratory, and immune diseases^[28]. The effect of *A. annua* specifically against malaria was elucidated by Y. Tu, who then purified one of its many active compounds, artemisinin (yu yu tu). She eventually received a Nobel Prize for her discovery. *Artemisia* extracts were used worldwide in various combinations^[31], for instance as an important constituent of Ji sing tea, which was widely used as a treatment for COVID in China^[25]. *Artemisia* spp extracts were specifically shown to have an *in vitro* effect on the replication of SARS-CoV-2^[32]. Yet, due to the lack of exact dosing and solid scientific proof of efficacy in RCTs, their employment was widely discouraged in many Western countries^[33].

These authors' own multi-year clinical and academic experience with *Artemisia* spp and appreciation of its safety (it is being used as herbal tea in many households in Israel) has led one of them to recommend it to multiple patients, together with breathing exercises, at early stages of infection by SARS-CoV-2. The rationale for this combined management approach was that by that time it was quite clear that the severity of the disease was an interplay between the virus and the immune system, whose dysregulation often led to a cytokine storm^[34]. Thus, the antiviral activity of *Artemisia* with its effect on the immune system seemed to be an optimal "package" for pharmacological treatment of COVID. It was also noticed that the rheological properties of the sputum of COVID patients were very similar to the viscous secretions seen in patients with cystic fibrosis (CF)^[35]. Therefore, it was recommended to add breathing exercises, such as those being used in CF patients. A short video tutorial and a brochure with suggestions for supportive care at the early stages of the illness were prepared and distributed via social media. It was stressed that the video and brochure do not replace consultation with a physician who is well acquainted with the patient.

To further evaluate the factors that may affect the severity of COVID, including the way in which patients elected to treat themselves, we initiated already at the early stages of the pandemic a trial based on patient-reported outcome questionnaires, as well as data extracted from patients' charts, when required. This study was approved by the Institutional Review Board of Kaplan Medical Center, and its results will be published separately. In this paper, we will concentrate only on those patients in the trial who reported the use of *Artemisia* extracts, in order to demonstrate how a plant extract can be beneficially used in situations in which there is no proven effective treatment for a potentially severe disease.

Overall, 75 patients reported using *Artemisia* extracts either in the form of a lukewarm drink or in steam inhalation, typically in conjunction with breathing exercises. None of these patients required hospitalization. Most were young with no underlying conditions, though 20 patients were older than 50 and 16 had at least one underlying disease. All had a relatively mild clinical course. 15 patients reported that they felt improvement in their respiratory symptoms and could expel disease-related phlegm more readily upon using *Artemisia*. The other patients who reported improvement in their condition used additional treatment modalities, such as vitamins and food supplements and therefore were not able to attribute it specifically to *Artemisia*. None of the patients had significant post-COVID symptoms and all fully recovered/returned to their baseline condition.

Below we will also briefly describe the clinical course of a few patients who demonstrated early signs of deterioration in their condition, such as a drop of O₂ saturation or a significant dyspnea, and reported a significant improvement upon using *Artemisia*.

-A 60-year-old woman who had undergone a lung transplant due to pulmonary fibrosis and was accordingly on immunosuppressive treatment, had mild to moderate dyspnea and a drop in her O₂ saturation to 90% within 2 days of contracting COVID. She started using food supplements and *Artemisia* as a lukewarm tea and steam inhalation in combination with breathing exercises. Within a few hours, she started coughing a significant amount of copious phlegm with a significant improvement in her respiratory symptoms and O₂ saturation. She continued to use *Artemisia* a few times a day. She further used *Artemisia* steam inhalation when she felt it was hard for her to expel phlegm. Under this treatment, she continued to have respiratory symptoms and intermittent drops in her O₂ saturation, but was stable and did not require any other treatment or hospitalization. She fully recovered back to her baseline within a few months.

-An 84-year-old man with multiple co-morbidities chose comfort care at home when he was advised to be hospitalized, as he had significant hypoxemia and bilateral consolidation in a chest x-ray. His daughter took care of him and started performing respiratory physiotherapy in combination with steam inhalation of *Artemisia*, every hour. Within a few days, there was significant improvement in his condition. He fully recovered back to his baseline within a few weeks.

-A 75-year-old woman, with no underlying disease, started using *Artemisia* and breathing exercises after a few days of her illness when she felt mild to moderate dyspnea with significant weakness, and her oxygen saturation dropped to 93%. Within hours she reported that her dry cough was changed to a productive cough, and she started expelling copious sputum. Her oxygen saturation returned to normal at 97%, but dropped again to the low 90s, within a few hours. She continued with hourly breathing exercises and *Artemisia* steam for the next few days, with a gradual stabilization of her respiratory condition. She fully recovered within a few months. She did not require hospitalization, supplemental oxygen, or respiratory support.

-A 59-year-old woman with neuromuscular disease had a significant dyspnea and worsening of her respiratory muscle weakness within a day of getting COVID, necessitating non-invasive ventilation support at home. She started using *Artemisia*, both as a lukewarm tea and steam inhalation, combined with respiratory physiotherapy by her caregiver a few times a day. She had intermittent drops in her oxygen saturation to the low 90s %, which improved with the treatment. She did not require increased respiratory pressure and did not require hospitalization. She had a significant improvement within 10 days and fully recovered back to her baseline after a few months.

A 58-year-old woman started to have significant respiratory symptoms a few days after contracting COVID. She initiated treatment with *Artemisia* and breathing exercises and called an ambulance that took her to the nearby hospital, where she was found to have an abnormal chest X-ray and oxygen saturation in the low 90s. She was started on steroids and continued with breathing exercises and *Artemisia* tea and steam inhalation. Within 2 days, there was a significant and unexpected improvement in her condition, and she was discharged. Within a week, she was fully recovered and was able to participate in strenuous physical activities.

The group of patients described above, even if quite small, showed evidence for a significant improvement in both objective (O₂ saturation and ease of sputum expulsion) and subjective (feeling of well-being) parameters, in response to the use of *Artemisia* extracts. Those were consistent with the mode of action of *Artemisia* as an anti-inflammatory and antiviral pharmacological agent. In addition, an interesting observation, not previously reported to the best of our knowledge, was that steam inhalation of *Artemisia* caused a change in the rheological properties of patients' sputum. Indeed, many of them reported a significant improvement in their ability to expel the "sticky" phlegm upon using this treatment modality. Importantly, *Artemisia* was well-tolerated also in a much larger group of patients, not described here in detail. Many of these patients reported experiencing a subjective improvement in their condition.

Medical practice should always be based on the assessment of risk vs. benefit for each specific patient, as well as each specific treatment modality. Based on this edict, and given that there had been no known proposed treatment at the early stages of COVID, the application of a herbal preparation possessing a very high safety profile and a potentially significant beneficial effect was a very reasonable approach. There are numerous papers in the medical literature discussing the clinical or *in-vitro* effects of *Artemisia* spp. on SARS-CoV-2. Thus, although this treatment modality was not tested in large-scale RCTs, there is enough evidence to support its use.

Why then has this and similar treatments not seen a more widespread use in the Western world? We believe that the reason for that was mostly the concern that they are not “evidence-based”, meaning that they were not tested in large-scale RCTs^[18] and that physicians would be considered as promoting “primitive” treatments and even quackery, instead of well-established modern treatments. The debate regarding the role of RCT-driven EBM in shaping our clinical decisions is not new^{[36][37]}, but the pendulum seems to be going strongly towards the EBM approach. We propose that the careful and thoughtful incorporation of herbal preparations into our practice, when deemed appropriate, will not lead to quackery, but rather to the exact opposite. Indeed, physicians who are ready to incorporate traditional treatment modalities, assessed in the light of modern science and medicine, are more likely to be able to provide their patients with a wider armamentarium and thus gain their trust, decreasing their need to search for alternative and less well-studied treatments elsewhere and their feelings of being abandoned by their physicians at a time of crisis^[26].

In conclusion, we have argued in this article that, although using RCT-driven evidence-based approaches have no doubt improved the quality of medicine, one should be cautious that the means does not become the end and that this excellent tool that aids us in our clinical practice does not become a Procrustean bed. Understanding the limitations of precision-driven medicine and carefully adding herbal treatments and food supplements, when there is no better management approach available, is not only desirable but can benefit both physicians and patients. We stress that the decision to use herbal preparations should be based on a sound knowledge regarding their safety and potential contraindications to their use, as well as knowledge of their clinical use in traditional medicine and a good understanding of their pharmacological activity in various medical situations. In case of doubt, it is always beneficial to consult a qualified herbal specialist regarding the amount and mode of administration. It is also important to verify the source of the plants, and whenever possible ready-made extracts should be obtained only from a qualified herbal pharmacy in order to ensure their quality and purity, as well as a reasonable level of standardization.

It is essential to understand that the utilization of herbal treatment approaches and sound scientifically proven EBM are not mutually exclusive. There is a growing body of knowledge that combines the tools of modern medicine and science with traditional medicine. There are also numerous studies regarding the interactions of various plants with commonly used medications. We call for more studies, including large RCTs, to assess both safety and efficacy of specific herbal preparations in various clinical situations, so that it would be possible to more readily incorporate them in the routine care of our patients. It should be taken into account, though, that the traditional treatment approach is not always suitable for statistically based RCTs, which are disease- and not patient-oriented, and some clinical situations call for a more holistic and patient-based approach. This is in fact addressed in the WHO guidelines for research on traditional medicine^[43].

Finally, we have to remember that the phrase “*primum non nocere*” was coined long before the era of RCTs, and that even many commonly used medications were not tested by this approach (such as pyridostigmine for myasthenia gravis and steroids for multiple clinical situations). This famous dictum implies that one should always be cautious when treating

patients and be aware of any signs that suggest more harm than good. However, it does not imply that one should give patients only medications that have gone through large-scale clinical trials and push aside all other human experience and knowledge.

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Footnotes

¹ <https://ods.od.nih.gov/factsheets/COVID19-HealthProfessional/#:~:text=Currently%2C%20data%20are%20insufficient%20to,prevent%20or%20treat%20COVID%2D19.>

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