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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Abstract

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 are reluctant to use herbal preparations, because there are no large-scale randomized controlled trials to support their use. In this paper, we challenge this approach and propose that herbal treatments should be added to our armamentarium, even if cautiously. This pertains to situations in which there is no existing well-studied evidence-based approach; 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, we share our knowledge and experience regarding the treatment of patients with COVID with the plant *Artemisia.*

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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 of those plants were used as treatment for human diseases. There are numerous examples of plant-based treatments in ancient Western medicine and in traditional Chinese medicine[3]. Some of these are being further studied and used as complementary treatments to this day[4]. 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 had received, etc. [5][6]

Although there are many levels of evidence, such as case series, small trials, and even case reports and *in vitro* studies, evidence-based medicine has become synonymous with large-scale randomized controlled trials (RCT). 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[7]. Second, the metabolism of drugs may vary between different patients[8]. 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. It should also be taken into account that a randomized clinical trial for a specific medicine 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 and can often inadvertently turn the patient into a jigsaw puzzle of seemingly unrelated problems.

It is true that most herbal preparations have not been tested in large-scale RCTs. Nevertheless, their safety has been assessed for hundreds of years[4]. Furthermore, there are certain clinical situations under which the utilization of crude plant extracts may be beneficial, even in modern countries. Indeed, such plants are readily available and may be a constituent in most kitchens or gardens, and there are no inactive ingredients that may cause adverse reactions[9].

Under which clinical situation is there a place for herbal treatments? 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, rather than taking the “wait and see” approach, it is conceivable to attempt treatment with an appropriate herbal preparation, based on the mode of action of its active ingredients. In addition, in the case of a refractory disease, one might try an experimental treatment (if it is available) or use an herbal preparation as part of the supportive care[10]. This may apply even to a new disease when it

lacks a known treatment.

A good example for such a situation is a pandemic caused by a novel virus, such as SARS-CoV-2. It was realized quite early in the pandemic that the rather insidious onset of the disease in most patients creates a possible window of opportunity to intervene at home when the patient has minimal symptoms [11]. Some physicians around the world attempted to use repurposed drugs, food supplements, and traditional herbal preparations in various combinations as a means to alter the course of the disease[12][13][14] Furthermore, many people around the world used food supplements and herbal treatments without any guidance from their physicians, who were reluctant to recommend such treatments without solid evidence-based data. In fact, the NIH created a list of such food supplements, with their safety profile and limited evidence for their efficacy based on small case series and clinical trials, adding that *Data are insufficient to support recommendations for or against the use of any vitamin, mineral, herb or other botanical, fatty acid, or other dietary supplement ingredient to prevent or treat COVID-19.* Thus, making the information available to the public while deterring physicians from recommending them to their patients. In this paper, we would like to focus on the plant *Artemisia*, as an example of a highly studied plant with well-established pharmacological activities which was used mostly in developing countries.

The genus *Artemisia* is one of the largest and most widely distributed genera of the family Astraceae (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 [15]. All *Artemisia* species contain pharmacologically active substances such as terpenoids, flavonoids, coumarins, caffeoylquinic acid, sterols, and acetylenes [16][17]. Numerous *in vitro* studies, as well as small-scale clinical trials, have shown their activity in infectious, malignant, respiratory, and immune diseases[15]. The effect of *A. annua* specifically against malaria was elucidated by Y. Tu, who then purified one of its many active compounds, artemisinin. She eventually received a Nobel Prize for her discovery. In the early days of the pandemic, *Artemisia* extracts were specifically shown to have an *in vitro* effect on the replication of SARS-CoV-2. . Yet, due to the lack of exact dosing and solid scientific proof of efficacy in RCTs, its employment was widely discouraged in many Western countries[18].

These authors' own clinical and academic experience with*Artemisia* 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. The rational for this 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, and that the cytokine storm was a result of a dysregulated immune system[19]. It was also noticed that the rheological properties of the sputum of the patients was very similar to the viscous secretions seen in patients with cystic fibrosis[20]. Thus, the combination of the antiviral activity of *Artemisia* with its effect on the immune system seemed to be an optimal "package" for treating COVID. A short video tutorial and a brochure with suggestions for supportive care in the early stages of the illness were prepared and distributed via social media. Data regarding the effect of artemisia on patients with COVID was extracted from A patient-reported study on COVID outcomes (approved by the institutional review board of Kaplan Medical Center, the results of which will be published separately).

Overall, 75 patients reported using *Artemisia* extracts either in the form of a lukewarm extract for drinking or steam inhalation, typically in conjunction with breathing exercises. None of these patients required hospitalization. Most were young with no underlying conditions, though20 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. The other patients used additional treatment modalities, such as vitamins and food supplements and therefore could not validate what helped. None had significant post-COVID symptoms and all returned to their baseline condition.

Below we will briefly describe the clinical course of a few patients who demonstrated early signs of deterioration in their condition, such as a drop of O_2 saturation or significant dyspnea and reported significant improvement when 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 luke-worm tea and steam inhalation in combination with breathing exercises. Within a few hours, she started coughing a significant amount of copious phlegm with significant improvement in her respiratory symptoms and O2 saturation. She continued to use Artemisia a few times a day and every time she felt it was hard to expel the 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 on CXR. His daughter took care of him and started doing 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 diseases started using artemisia and breathing exercises after a few days of her illness when she started even mild to moderate dyspnea, 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-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. She had significant dyspnea and worsening of her respiratory muscle weakness within a day of getting COVID, necessitating NIV support at home. She started using Artemisa, both as a lukeworm tea and steam inhalation, combined with respiratory physiotherapy by her caregiver a few times a day. She had intermittent drops in her oxygen saturation in the low 90s, which improved with the treatment. She did not require increased respiratory pressure and did not require hospitalization. She had significant improvement within 10 days and

fully recovered back to her baseline after a few months.

A 58-year-old woman who started to have respiratory symptoms a few days after contracting COVID. She started treatment with artemisia and breathing exercises and called an ambulance which 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 able to participate in strenuous physical activities.

The patients described above showed evidence for significant improvement in both objective (O_2 saturation and ease of sputum expulsion) and subjective (feeling of well-being) parameters, which were consistent with the mode of action of *Artemisia* as an anti-inflammatory and antiviral pharmacological agent. This treatment approach 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, although objective measures were lacking.

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 was no known proposed treatment at the early stages of COVID, the application of herbal preparations possessing a very high safety profile and a potentially significant beneficial effect was a very reasonable approach. There are over 1000 papers in the medical literature regarding the clinical or in-vitro effects of different types of artemisia on SARS-CoV-2. Thus, although this treatment modality was not tested in large-scale RCTs, there was enough evidence to support its use.

Why then have such treatments not seen a more wide-spread 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 evidence-based medicine (EBM) in shaping our clinical decisions is not new[21][22], 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 feel abandoned by their physicians at a time of crisis[23].

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 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, when using ready-made extracts, it is important that those will be obtained from an herbal pharmacy, in order to ensure their quality, purity, and a reasonable level of standardization. It is also important to understand that utilizing herbal treatment approaches is not mutually exclusive to sound scientifically proven evidence-based medicine. There is a growing body of knowledge which combines the tools of modern medicine and science with traditional knowledge. There are also numerous studies regarding the interactions of various plants with commonly used medications. We call for more studies, including large randomized clinical trials that assess both the safety and efficacy of specific herbal preparations in various clinical situations, so that we can more readily incorporate them into the routine care of our patients.

We also think that during a pandemic with a novel virus for which there is no proven treatment, it is important to explore all possible management approaches, as long as they are known to be safe, even if, at the time, there are no large-scale RCTs to prove their efficacy.

Finally, we have to remember that “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 mestinon for myasthenia gravis and steroids for many 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 only 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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