

## Complementary and alternative medicines use in COVID-19

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## **[Commentary]**

### **Complementary and alternative medicines use in COVID-19: a global perspective on practice, policy and research**

#### **Introduction**

Since the first cluster of cases identified in December 2020 in Wuhan China, COVID-19 was declared a global pandemic in March 2020. As of April 2021, the pandemic has caused over 3 million deaths globally.<sup>1</sup> Currently, the approved vaccines and public health prevention measures such as social distancing, hand hygiene, contact tracing, and lockdown policies remain the mainstay of COVID-19 mitigation measures.

While the emergence of effective vaccines has offered the Governments, scientific communities, and members of the public a hope out of the pandemic, effective pharmacotherapy, including immunotherapy for COVID-19 prevention and treatment, is yet to be established. Some of the early treatments recommended for COVID-19 treatments, including hydroxychloroquine, and remdesivir have demonstrated limited effectiveness in early clinical trials.<sup>2,3</sup> Currently, steroids, including dexamethasone, remain the only treatment proven to be effective in clinical trials in terms of mortality and hospitalization outcomes.<sup>4</sup> Patients and members of public across the world are known to be relying on self-care practices including the use of Complementary and Alternative Medicines (CAM) for COVID-19 prevention and symptoms relief.

CAM refers to broad sets of practices, which are not fully integrated into the dominant healthcare system and can include herbal treatments, yoga, and relaxation techniques.<sup>5</sup> These have been used by diverse communities across the world for thousands of years for the prevention and treatment of long-term health conditions and acute illnesses such as the treatment of respiratory infections. A recent systematic review of CAM use in diabetes listed over 37 different CAM types and 223 herbs used by patients.<sup>6</sup> It is estimated that up to 70% of the low and middle-income countries (LMICs) are known to rely partly or entirely on the use of CAM to treat their health problems.<sup>7</sup> Over 50% of the 194 WHO member states are currently known to have a national policy on CAM use (WHO).<sup>8</sup>

Given the lack of adequate pharmacotherapeutic approaches to COVID-19, a surge in demand for the information and CAM products has been noted in the popular media. A recent study on the impact of the COVID-19 pandemic on clinical pharmacy practice suggested pharmacists being increasingly requested information about dietary supplementation, vitamins, and any options on the shelves that could offer symptom relief and boost immune system.<sup>9</sup> This narrative will aim to discuss global practices and policies in regards to CAM use in COVID-19. A global

update will enable understanding of international practices and policies, patient and consumer behaviors, identification of popular CAMs and those tipped for potential benefits, including evidence base, and thereby support counselling and communications by healthcare professionals when patients present for advice. The following section will summarize information relevant to different geographical regions with a historical, religious, and cultural association with CAM use.

## **China**

Traditional Chinese Medicines (TCM) have been utilized extensively in treating COVID-19 patients in China during the outbreak. Personalized treatment through syndrome differentiation, unique characteristics of TCM, is appealing to clinicians. Syndrome differentiation is a summary of the pathological signs of the body at a specific stage during disease development, based on the synthesized data collected with the four diagnostic methods: observation, listening and smelling, asking, and palpation and pulse-taking.<sup>10</sup> Thus, TCM is recommended as a COVID-19 treatment option in the China National Health Commission (NHC) guidelines.<sup>11</sup>

Currently, 15 TCMs are recommended with seven oral formulations (Angong Niuhuang, Zixue, Huoxiang Zhengqi, Jinhua Qinggan, Lianhua Qingwen, Shufeng Jiedu, and Fangfeng Tongsheng), and eight injectable formulations (Xiyanping, Xuebijing, Reduning, Tanreqing, Xingnaojing, Shenfu, Shengmai, and Shenmai). The China Food and Drug Administration (CFDA) has approved Xuebijing with a treatment indication of 'new coronavirus pneumonia with severe and critical systemic inflammatory response syndrome or/and multiple organ failure', and Lianhua Qingwen with a new indication of 'treating for fever, cough, and fatigue caused by the light and ordinary types of the new coronavirus pneumonia'.<sup>12</sup> Each TCM formulation contains several active ingredients with proven multi-target effects, making it challenging to develop drug resistance. Many TCM formulations also possess potent anti-inflammatory and immunomodulatory effects. TCM clinical pharmacists play an active role in reviewing TCM prescriptions, preparing TCM decoctions, therapeutic monitoring, patient education, science popularization, and clinical research.<sup>13</sup> Numerous trials are currently taking place in China assessing the effectiveness of the products in COVID-19 treatment.<sup>14</sup>

## **South Asia**

The use of CAM is widespread and is culturally embedded in the countries belonging to the South Asian region, including Pakistan, India, Bangladesh, Nepal, Sri Lanka, Afghanistan, Bhutan, and Maldives.<sup>15-17</sup> A study from the COVID-19 isolation center in India suggested that over a quarter (25.8%) of patients used CAM during their treatment and afterwards.<sup>18</sup> CAM practices prevalent in the area include Ayurveda, Unani, Reiki, Homeopathy, Biochemistry, and Aromatherapy. For example, since the beginning of the Indus civilization, Pakistan has a

long history of using herbal medicines. Up to 80% of the population use CAM, including herbal products, in their daily practice.<sup>16</sup> Traditional medicine-based therapy, including Unani and homeopathic systems, is considered a vital source of healthcare in the region, especially in rural areas, where CAM serves as the first line of therapy.<sup>15, 16</sup>

Culture, lack of access to modern medicines, and cost considerations are essential factors of CAM use in South Asia. CAM is embedded in the policy and healthcare practices in the region. For example, in 2001, “Traditional and Complementary Medicines” was included and adopted in Pakistan’s National Health Policy.<sup>8</sup> The Indian Ministry of Health has established the Ayurveda, Yoga, Unani, Siddha, and Homeopathy, namely AYUSH (Ayurvedic, Yoga, and Naturopathy, Unani, Siddha, and Homeopathy) department that was later formed as Ministry of AYUSH in 2014 which has produced specific COVID-19 prevention and treatment guidelines for CAM practitioners.<sup>19</sup> The guidelines advocate the use of yoga and herbal products such as *Embilica officinalis* (Indian gooseberry), *Ocimum tenuiflorum* (basil) and some branded herbal formulations as immune boosters. Other herbs of relevance in South Asia include curcumin, quinine, and echinacea for their respective antimicrobial, antiviral, anti-inflammatory, and immuno-booster activities.<sup>20</sup> Limited evidence, however, has been published in relation to effectiveness of such herbal remedies. In vitro studies in India demonstrated *Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Giloy), and *Ocimum sanctum* (Tulsi) linked to protease inhibition activities of SARS-CoV-2 virus.<sup>21</sup> In addition, the World Health Organization (WHO) has acknowledged the effectiveness of *Artemisia annua* (a medicinal plant- abundantly available in both India and Pakistan) as a potential pharmacotherapy research candidate against COVID-19.<sup>22, 23</sup>

## **Middle East**

CAM is commonly used in the Middle East because it is linked to Islamic history with herbal treatments mentioned in Quran and is often known in the region as ‘Arabic’ or ‘Islamic’ medicine. CAM use is expected to grow at a compound annual growth rate of 22.8% from 2020 to 2027.<sup>24</sup> Since the pandemic reached the area CAM use is known to be common in the region.

In a recent study conducted in Saudi Arabia, over 1 in 5 (22.1%) of the 5258 survey respondents acknowledged their use of herbal products during the pandemic period because they believed that they are effective for the prevention of COVID-19.<sup>25</sup> Meditation or holy Quran recitation, cupping therapy (Hijama), acupuncture, massage, specific nutritional tonics, and herbs such as honey, dates, figs, peaches, garlic, olives, *Anthemis hyalina* (chamomile) and black cumin seeds are amongst the CAMs used for prevention and relief of symptoms include fatigue, loss of smell and breathing difficulties linked to COVID-19.<sup>26</sup> *Nigella sativa* when combined with grinded *Anthemis hyaline* and honey (TaibUVID was referred to prevention and treatment potential.<sup>27, 28</sup> Other herbal products described in the literature include garlic, onions, and ginger preparations.<sup>29</sup>

Several clinical trials on CAM have been registered in the Middle-east, notably, the phase II trial in Israel on the phytocannabinoid cannabidiol.<sup>30</sup> It is a non-psychotropic constituent of *Cannabis sativa* and possesses potent anti-inflammatory and immunosuppressive effects. These effects are mediated through the inhibition of proinflammatory cytokine release and stimulation of anti-inflammatory cytokine production.<sup>30</sup> A clinical trial in Egypt aims to evaluate the therapeutic potential of liquorice extract and *Boswellia serrata* gum.<sup>31</sup> These plants are reported to have anti-inflammatory, antiviral, antithrombotic, and immunomodulatory properties.<sup>32, 33</sup> A clinical trial in Iran aims to assess the effectiveness of colchicine combined with, herbal phenolic monoterpene fractions.<sup>34</sup>

## **Africa**

The WHO estimates that more than 80% of the African populations rely on traditional medicine for their healthcare needs.<sup>35</sup> Traditional medicine has continued to gain acceptability in Africa due to its low cost, availability, and perceived low toxicity.<sup>36</sup> There is a lack of adequate data on the use of CAM during the COVID-19 pandemic in Africa. Recently the Madagascar Institute of Applied research linked the use of *Artemisia annua* (sweet wormwood) in COVID-19.<sup>37</sup> *Artemisia annua* is the source of antimalarial drug artemisinin. Potential widespread use has raised concerns amongst the scientific community in regards to malarial resistance to the drug.<sup>38</sup> Leaves of *Azadirachta indica*, *Mangifera indica*, *Eucalyptus globulus*, *Carica papaya*, *Psidium guajava*, *Citrus reticulata*, and *Musa paradisiaca* steam-inhaled and taken orally were shown in a recent study to be offering symptoms relief and restore physiological and psychological functions.<sup>39</sup> Zimbabwean government was reported to have authorised herbalists to treat patients with COVID-19 symptoms raising concerns among national public health experts.<sup>40</sup>

## **South America**

Herbs and spices are very commonly used in Latin American countries. For example, in Brazil, the sales value of herbal drugs reached USD 187 million in 2019, a 3% annual growth compared to the previous year.<sup>41</sup> *Mikania glomerata* preparations have been known to be used in South America to treat respiratory illnesses such as cough and asthma. Bronchodilator action of the herb has been suggested.<sup>42, 43</sup> These are widely used and prescribed in Brazil, including their use in children.<sup>44</sup> Propolis produced by bees and commonly found in Brazil and exported to Asia including China, has been tipped to potentially interfere with host cell invasion by SARS-CoV-2.<sup>45</sup>

Indigenous communities in South America have also been reported to be using CAM during COVID-19. For example, herbal teas and root teas were reported to have been used by Dâw Indigenous communities in Brazil.<sup>46</sup> Anecdotal reports of patient experience suggested that they perceived the teas to have helped them cope with the symptoms.<sup>46</sup> A consortium of Latin-American and Caribbean Center has joined efforts in synthesising the evidence base in regards

to herbal medicines use in COVID-19.<sup>47</sup> Other herbs mentioned to have been used by Ecuadorian Amazon tribes include umu'co or cat's claw as antipyretic; wild ginger as a cough reliever, and cinchona bark as anti-inflammatory.<sup>48</sup>

## **Europe and the North America**

CAM practices amongst communities in Europe and North America are diverse, reflecting the cultural diversities in these countries. In the US alone, it is estimated that over 20,000 different types of herbal products are available.<sup>49</sup> Herbal products regulations across Europe and North America are, however, varied. The US Food and Drug Administration (FDA) classifies herbal preparations as food supplements, and these herbal products do not require pre-marketing authorization from the FDA. However, such products should satisfy pre-marketing laws in Europe.<sup>50</sup> This includes adherence to criteria in regards to manufacturing and storage standards in Europe.

Anecdotal reports have suggested a surge in demand for TCM in the West during the initial phase of the pandemic leading to wholesale suppliers deciding to ration the supply to the retailers.<sup>51</sup> In a study conducted in Norway with CAM practitioners, relaxation techniques, prayers, ginger, and fish oils were some of the key practices they recommended to service users. Over 40% of the CAM practitioners in the study admitted that they would not refer COVID-19 patients for treatment by a physician.<sup>52</sup> In the UK, herbs being sold as 'immunity boosters' against coronavirus were reported, which was considered against legal practice given the lack of evidence through clinical trials.<sup>53</sup>

Currently, limited research is being undertaken in the Europe and the North America to identify the effectiveness of CAMs including herbal medicines. Models of nano-fibre-based respiratory masks with herbal ingredients to minimise infection rates have been suggested.<sup>54</sup> Herbal products previously tipped to inactivate the Severe acute respiratory syndrome (SARS) virus and dengue fever, such as *Andrographis paniculate* are known to be amongst those being investigated.

## **Discussion and conclusions**

Currently, the use of CAM in COVID-19 seems to be a common practice, globally. In particular, a range of herbal products across different geographical regions and continents are perceived by users to be effective in symptoms relief and/or treatment. Many governments have also formally or informally advocated or authorised the use of CAM in COVID-19, mainly based on their effectiveness in alleviating other respiratory symptoms or in some occasions on popular beliefs. CAM use in COVID-19 also reflected geographical, cultural, and religious practices.

Currently, limited research exists from human clinical trials in regard to the effectiveness of CAM in prevention, treatment, or symptom relief in COVID-19. In addition, gathering patient perspectives and experiences of CAM use in COVID-19 are imperative in informing future practices. Gathering data on common information queries received in community pharmacies, other healthcare settings and those described in internet forms will enable the development of evidence based information sources that can support effective patient counselling and communication practices.

At this time international clinical guidelines do not proactively encourage healthcare professionals to investigate patient use of CAM. It is known that up to 2/3<sup>rd</sup> of CAM users do not declare their CAM use with healthcare professionals.<sup>6</sup> COVID-19 patients, particularly with comorbidities and using medicines for long-term conditions, can benefit from evidence-based guidelines in regards to drug-herb or herb-disease interactions.

The COVID-19 pandemic has met international health systems with a low level of preparedness and emergency response. Healthcare professionals, including pharmacists, are likely to be sought advice and counselling regarding the use of CAM. Pharmacists have been traditionally offering services for self-care and common ailments including supply of non-prescription medicines.<sup>55-57</sup> It is imperative that counselling and communications practices by healthcare professionals, including pharmacists, in regards to CAM use are evidence based. Phytochemicals have been integrated into the treatment of long-term health conditions such as cancer and gout. More extensive scientific evidence needs to be sought for their use in COVID-19.

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