



Review Article

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A REVIEW AND UPDATING OF THE KNOWLEDGE OF BIOCHEMICAL MECHANISMS OF PERFORMANCE ACTING SOME SPICES & MEDICINAL HERBALS FROM AYURVEDA PROTOCOL VS COVID-19

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ABSTRACT

The publication and worldwide diffusion of the Ayurveda treatment of COVID-19 and the vital role that spices, and medicinal herbals play in this protocol, promoted by the Department of Health and Family Welfare of India (MoHFW), in the context of SARS-CoV2 infection. Encourage us to review updating the knowledge of these herbals' plants' biochemical mechanisms of action. Several biochemical mechanisms of action of spices have been studied and established in the context of COVID-19. It has been described that herbs act as blocking agonists of some cell receptors, such as the ACE2 receptor of the renin-angiotensin system and TRP receptors belonging to the superfamily of sensory neurons, responsible for symptoms the SARS-CoV2 virus. We also find widely recommended medicinal herbs such as *Tinospora cordifolia* and *Withania somnifera* in this protocol, which has been described to stimulate the immune system and, at the same time, increase the destructive capacity of macrophages and biochemically block the entry of SARS-CoV-2 to host cells. Other medicinal herbs recommended by the Ayurveda protocol such as *Curcuma longa* L, *Cinnamomum camphora*, *Eucalyptus globulus*, *Allium sativum* L, *Piper nigrum*, *Glycyrrhiza glabra* L, as well as being potent antioxidants and anti-inflammatory are traditionally selected as an adjuvant treatment indicated for "respiratory diseases" as in the current framework of the COVID-19 pandemic. This article explores the Ayurveda protocol and some recently recommended nutraceutical substances and spiced dietary guidelines, as an alternative treatment in concern to SARS-CoV2 infection, for the treatment of long-term side effects of the post-COVID syndrome.

Keywords: Spices, Medicinal Herbal, Ayurveda, COVID-19, SARS-CoV2

INTRODUCTION

The recent publication of the official recommendations for the treatment of COVID-19, proposed by Ayurvedic medicine promoted by the Department of Health and Family Welfare of India (MoHFW) and the Ministry of AYUSH^{1,2}, constitutes an official recognition of this alternative medicine, popularly followed, and practiced in India and some Eastern countries for centuries. Among these guidelines stand out the use of spices and medicinal herbals.

The use of Ayurvedic medicine to reduce the symptoms of common colds, as well as non-allergic rhinitis and other pathologies^{3,4,5}, have been known and used in these eastern populations for millennia which supports it in the current context for its use also in the prevention and treatment of SARS-CoV2, as a modern but millenary medicine based on evidence (Cochrane)⁵.

Among these spices, Turmeric stands out. It has been described that it is obtained from the rhizome of the *Curcuma longa* L. Its main active component is a phenol called curcumin, a spice used in many eastern countries for culinary and food colouring purposes⁶. Several monographs have also been published regarding its potential in treating COVID-19^{7,8} and its use has recently been approved by the FDA (E.U. Food and Drug Administration)⁹. Between the Ayurveda protocol, we can find a ginger (*Zingiber officinale*), composed of essential oil, the gingerol, eucalyptus (*Eucalyptus globulus*), being 1-8 cineol

(eucalyptol) the majority component, and black pepper (*Piper nigrum*) with piperine as the active component, camphor (*Cinnamomum camphora*), glycyrrhizin (*Glycyrrhiza glabra* L), and other spices such as garlic (*Allium sativum*), Cinnamon (*Cinnamomum zeylanicum*).

Finally, we find medicinal herbs such as Guduchi (*Tinospora cordifolia*) and Ashwagandha (*Withania somnifera*)^{10,11} widely recommended in the Ayurveda protocol, in particular for the alternative treatment to boost immunity with no side effects concerning COVID-19. Special mention in this review deserves the interaction between spices since consuming several mixed herbs is common. The potentiating power of piperine and curcumin has been described and studied in several research articles^{12,13}. All these spices have been popularly used for the prevention and treatment of other viral infections, as such respiratory syncytial virus, herpes zoster, non-allergic rhinitis, and bronchial asthma for centuries^{5,14,15,16}. Currently, spices and medicinal herbals and their possible mechanism of action are intensely studied by virtual screening, molecular docking^{17,18}, systematic review and meta-analysis^{19,20} and research articles^{21,22,23,24}, randomized controlled pilot study^{25,26} and clinical assays²⁷ for the treatment and prevention of COVID-19.

This work studies the role of spices and medicinal herbals in the Ayurveda protocol and their mechanisms of action related to SARS-CoV2 infection. The validity of these protocols is analyzed as alternative treatments for COVID-19 and the secondary effects of persistent or COVID- Syndrome²⁸.

Bibliographic review

A systematic review, without meta-analysis, has been carried out following the Prisma guide 2020 (<http://www.prismastatement.org>). We conducted an exhaustive search in the scientific literature and medical databases in English and Spanish, such as PubMed, Medline, OldMedline, Cochrane, Embase, WoS, Bireme, Lilacs. The research strategy includes all the studies that seek the association between the terms or keywords used for the query: piperine, curcumin, garlic, ginger, cinnamon, eucalyptol, camphor, glycyrrhizin, Guduchi, Ashwagandha, Ayurveda medicine, COVID19, SARS-CoV2.

The selection period of the articles was unlimited (until the date of sending our paper), focusing mainly on the period of the pandemic (2019-2022). It has been carried out by the two authors of this work independently and finally contrasting the concordance of the different options. All references have been managed using reference management Mendeley software.

RESULTS

In the initial phase of COVID-19 infection (0-10 days), when the patient meets a virus carrier, SARS-CoV2 enters the patient's respiratory system. It fixes on the oropharyngeal cells, using and exploiting the cellular receptor (ACE2), belonging to the renin-angiotensin system of the cell. The virus enters the cell, and after various biochemical processes, the cell replicates the virus's genetic material, which spreads to other cells of the respiratory system²⁹. The massive and spurious utilization of the oropharyngeal cell receptor (ACE2) by SARSCoV2 causes a biochemical imbalance in the cell's angiotensinogen-angiotensin converting system, producing an increase in oxidative and pro-

inflammatory peri-cellular stress due to the secretion of cytokines³⁰. The progression of the virus in the patient (10-20 days) triggers an increase in oxidative stress in various organs and the appearance of "cytokine storm syndrome"³¹, which causes an increase in the so-called cytokines that can, in some cases, for example in patients with specific secondary comorbidities such as diabetes, heart failure, etc., leading the patient to multi-organ failure and exits²⁹. It has also been described that intestinal dysbacteriosis with a decrease in prebiotics such as Lactobacillus and Bifidobacterium can occur in COVID patients with clinical digestive complications, such as diarrhea and acute dehydration³².

For its antioxidant and anti-inflammatory properties, turmeric in Ayurvedic medicine has been well known for centuries. Nowadays, it has been proposed in the preventive and curative treatment protocol of COVID-19 (MoHFW), Ministry of AYUSH^{1,2}. Currently, some research work is being carried out to know the mechanism of action of curcumin, the major component of turmeric. Curcumin's anti-inflammatory property is due to the capability for the modulation of NF-κB (transcription factor), reduce the pro-inflammatory cytokines (IL-2, IL- 8 IL-1B), down-regulate enzymes such as 5-lipoxygenase and COX-2 and COX-5 and finally mitigate "la cytokine storm syndrome " concerning COVID-19^{7,8}. Curcumin was also seen to act as an agonist by blocking the spike protein ACE2 receptors on which SARS-CoV2 binds, competitively inhibiting the entry of the virus into the cell. Finally, it has been described that curcumin may hinder the replication of SARS-CoV2 through protease inhibition of the Main Protein (MPro) and protein S (Spike receptor) of the virus, and its release from infected cell^{7,8}. In summary, it has been shown that curcumin has antiviral and antioxidant action. Its use as a food supplement could be considered especially beneficial in treating persistent COVID^{7,8,28}.

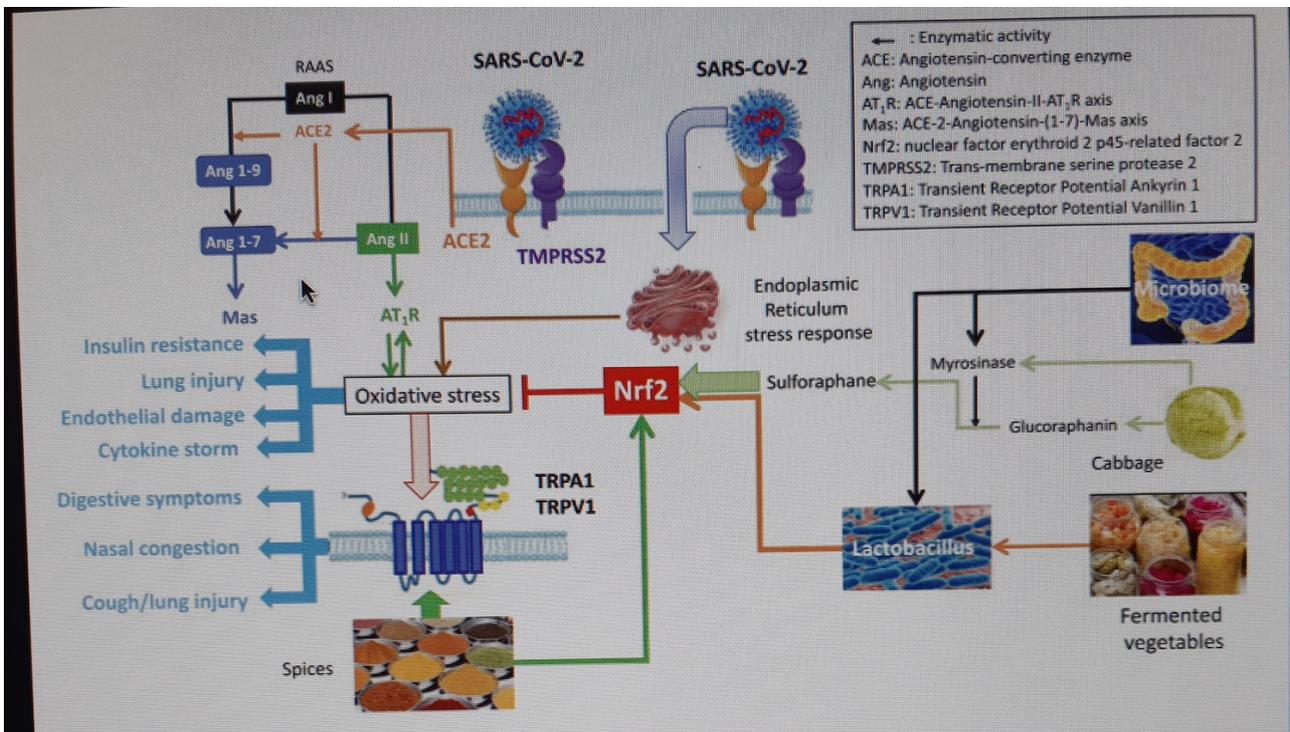


Figure 1: Interactions between foods and COVID-19. ←, enzymatic activity; ACE, angiotensin-converting enzyme; Ang, angiotensin. AT1R, ACE-angiotensin-II-AT1R axis; Mas, ACE-2-angiotensin-(1-7)-Mas axis; Nrf2, nuclear factor erythroid 2 p45-related factor; TMPRSS2, transmembrane serine protease 2; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanillin 1; ER, endoplasmic reticulum.

The bibliography shows us various research articles to measure the specific actions of certain spices, such for example quantifying the activation effect of the nuclear factor derived from erythroid (Nrf2), which is the most potent antioxidant substance in the circulatory system^{33,34,35,36}, or measuring how spices can act as potent agonists at TRPA1 / V1 receptors, such as allicin, allyl- isothiocyanate, cinnamon, wasabi, pepper (potent TRPA1 and Nrf2 agonists)^{24,37,38}, as well as capsaicin (TRPV1 agonist)^{5,39} (Figure 1). All species were rapidly effective (1 - 10 minutes), but their effect disappeared within 1 to 4 hours. These works suggest rapid desensitization of TRPA1 / V1 and that the duration of action of the compounds was concise; in addition, short-lived coughing episodes were recorded during the provocations, suggesting receptor desensitization-resensitization^{5,37,48}. The results of these clinical assays described are not conclusive evidence. More complementary studies are needed with a statistical number of samples, but they show us the varied mechanisms of action of spices anyway.

Several works have described some mechanisms of action of other spices included in the Ayurveda protocol, piperin, which has also been shown to interact with the mechanisms of cellular autophagocytosis⁴⁰. Other spices and medicinal herbs, such as curcumin and Glycyrrhiza glabra, inhibit some proteases of the SARS-CoV2 virus, such as Mean protein (Mpro) and protein S (Spike receptor), which are essential for the synthesis of virus capsid proteins, thus preventing virus replication in cells and reducing their rapid spread^{7,8,41,42}.

On the other hand, about to some medicinal herbs widely recommended in the Ayurveda protocol, such as *Withania somnifera*, also known as Ashwagandha and *Tinospora cordifolia* (Guduchi), it has been described that their mechanism of action is by stimulating the immune system and increasing the destructive ability of macrophages, responsible for fighting microbial and virus invasion^{10,11,43,44}.

Another aspect to consider is the interaction effect between several spices since the joint use of several herbs is an everyday customer. This interaction has been described with spices such as piperine. This effect was observed in a research assay when piperidine and curcumin were co-administered in humans. After this combination, there was an increase of up to 2000% in plasma concentrations of curcumin, so it was deduced that piperine potentiates the effect of curcumin^{6,12,13}. This potentiating effect is well known in Ayurvedic Medicine, which uses it in many of its protocols^{4,25}, among which the current preventive and curative treatment of COVID-19 stands out^{1,2}.

Finally, the literature reveals that some spices have been traditionally used as a remedy for the common cold⁴ and to alleviate the symptoms of non-allergic rhinitis⁵, they could act through other mechanisms such as "tachyphylaxis", which could be defined as the disappearance of the response to various applications of agonist substances,^{5,37-39}. Furthermore, certain spices could block cell receptors preventing the activation of TRPA1 and TRPV1 by SARS-COV2 and mitigate or reduce vagus or sensory nerve discharges that produce clinical symptoms of COVID-19, such as coughing and sudden and severe loss of smell and taste^{22,24,28,51}.

In summary, the use of spices would be indicated and justified in treating COVID-19 as an alternative medicine based on evidence^{4,5,15,16}. In addition, the high doses of herbs that are regularly consumed in sub-Saharan countries and Asia could represent a modulating factor of the SARS-CoV2 infection and could explain the low initial mortality rates in these countries in the COVID-19 pandemic⁴⁵⁻⁴⁷.

Consequently, all these experiences have contributed to the development of "a proof of concept" to hypothesize that foods combined with spices may be beneficial in alleviating some symptoms of COVID-19⁴⁶⁻⁴⁹. However, before these treatments can be recommended for SARS-COV2, more complementary clinical trials are needed to evaluate the benefits of spices through double-blind ecological studies of selected communities that regularly consume these spices in their diet.

DISCUSSION

Several studies have described the general mechanisms of action of certain spices, such as, for example, the spices that act interacting between viral-Spike(S)-Protein receptor binding and host ACE2 cell receptor, preventing the virus from fixing in the cell and its subsequent entry and replication^{6,21,24,44}. The spices also act by blocking TRAPA1 / V1 cell Receptors (allicin, pepper, eucalyptol, capsaicin, wasabi, cinnamon), and their consumption reduces the clinical symptoms and severity of the disease of COVID-19^{22,24,49}.

Other authors, however, have described alternative mechanisms to explain the desensitization of these cell receptors, such as "tachyphylaxis", which is defined as a decrease or cancellation of the response to the repeated application of agonist substances. Certain species could block cell receptors preventing the activation of TRPA1 and TRPV1 by SARS-COV2 and mitigate or reduce vagus or sensory nerve discharges that produce clinical symptoms of COVID-19, such as coughing and sudden and severe loss of smell and taste^{24,28,51}. The blockade of these receptors could be necessary, as proposed by Ayurveda medicine treatments, to reduce the symptoms of certain diseases such as influenza⁴, nonallergic rhinitis⁵, respiratory syncytial virus¹⁴, or bronchial asthma¹⁶.

The spices with beneficial effects for humans that stand out are capsaicin, curcumin, allicin, piperine, wasabi etc.^{3,22,24,49,50}. Most of them have a potent antioxidant activity through different systems such as indirect or sometimes direct activation of nuclear factor (derived from erythroid 2)-like 2 (Nrf2)³³⁻³⁶, and they are also TRP (Transient Receptor Potential) agonists³⁷⁻³⁹. However, some spices can interact with SARS-CoV-2 with other mechanisms such as, for example, protease inhibition of SARS-Cov-2 Main protein (Mpro) and protein S (Spike receptor), preventing the intracellular replication of the virus and its extension to other cells^{7,41,42}.

In addition, several authors have established that there could be a certain relationship synergy between diet and cell receptors TRPA1 / V1 and nuclear factor (derived from erythroid 2)-like 2 (Nrf2)³⁴⁻³⁶, which could explain the low mortality rate in some Sub-Saharan and Asian countries with high consumption of spices in their usual diet, at the beginning of the COVID-19 pandemic^{24,45,46,47}. Consumption of foods with a large number of herbs can desensitize TRP channels. At the same time, the antioxidant action of these spices would activate the Nrf2 pathway and reduce or mitigate "the cytokine storm syndrome" phenomenon (Fig 1), which can cause extreme morbidity and mortality in people of advanced age and with specific secondary comorbidities such as obesity and diabetes in COVID-19²⁹⁻³¹.

On the other hand, it should also be considered that the mechanism of action of some spices and medicinal herbals can be multifactorial and multitasking, activating several mechanisms of action at the same time^{11,21,24,34,38,40,41}. For example, such as some medicinal herbals, Guduchi and Ashwagandha, are widely recommended in the Ayurveda protocol, which has been described to stimulate the immune system and, at the same time,

increase the destructive capacity of macrophages and, in addition, biochemically block the entry to SARS-CoV-2 into the host cells^{10,11,21,43,44}.

There are significant variations between countries in mortality rates from COVID-19, which could be partly explained by diet. Many countries with low death rates from COVID-19 use large amounts of various spices as a common feature^{24,45,46}.

In this work, recent publications referring to the role of spices concerning COVID-19 have been described, which often show contradictory arguments to explain the mechanism of action of the same spices. The explanation for this disparity of criteria could be that, given the diversity of the substances included in the denomination of spices³ and that sometimes a mixture of substances from drying is called spices scratch a root, such as "turmeric", being this in turn consumed together with other spices for example in India and other Eastern countries,^{3,6,22,24,49}.

For these reasons, scientific articles referring to the study of the therapeutic effects of spices or medicinal Herbals are analyzed^{22,24,49,50}. Often they are confusing since it is difficult to reproduce their results because they may depend on the purity of the extract used, its geographical origin and if the spices are mixed with other herbs or substances, and often the routes of administration used, for example, gargles and intranasal application are not specified^{22,48,49,50}.

In short, the beneficial role of spices in the preventive and curative treatment of COVID-19 is undoubted^{19,20,22,49,50}. Administration of the herbs and herbals extracts can reduce or mitigate clinical symptoms^{22,24,48-50} and have an effective result on health by boosting the immune system^{10,11}. Finally, the successful introduction of the Ayurveda protocol in treating persistent COVID-19 to mitigate long-term side effects as alternative medicine has been widely accepted by medical staff^{28,51-53}. However, the benefits of the spices must be evaluated through ecological studies of certain consuming communities of herbs in their habitual diet, and these studies must be statistically designed in a double-blind manner with their corresponding placebos to obtain significant results to be able to go, from "empiricism to the science".

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