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Review Article

Role of Spices in Offering Natural Immunity to Fight Various Diseases

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ABSTRACT

Adequate nutrition intake is one of main factors to strengthen immunity. Traditional and cultural practices of food consumption involve use of several spices in limited quantities as part of food. Spices have offered versatile biological effects due to presence of valuable biochemicals. The aim of the present paper is to review published scientific evidence on potential role of spices in offering innate and adaptive immunity to human body. It has been demonstrated that, turmeric, one of the widely used spices, acts as an anti-viral agent through inhibition of viral entry into cells, suppression of viral replication and modulation of cytokines. A field study revealed that nations with higher consumption of spices have shown lesser COVID-19 cases and higher recovery rates. Further, spices also have shown to possess antioxidant activity superior or equivalent to ascorbic acid and are known to regulate inflammation processes. Evidence generated from the published literature is compelling to arrive at a conclusion that consumption of spices might improve immunity there by offering protection against various diseases including COVID-19. It is also noted that there are lesser number of human clinical trials in this area which warrants immediate attention to provide scientific evidence to immunity offered by spices.

Key words: COVID-19, Spices, Immunity, Diet, Nutrition.

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INTRODUCTION

Traditional foods, traditional medicines and Ayurveda (Indian system of medicine) have long history of safe use to maintain health. It is a holistic approach which means that they target root cause of disease but not symptoms. They offer preventive care strengthening body's immunity to fight disease. Underlying principle of helping to maintain health is by boosting body's natural defense system. Consumption of spices and condiments in small quantities as a part of diet on a regular basis has been proven to strengthen body's immunity. A detailed account on various traditional foods and the global regulatory guidelines were published.[1]

During early stages of COVID-19 (coronavirus disease-19) pandemic, Ministry of Ayush, Government of India issued guidelines and prescribed usage of spices in order to develop body's natural defense system. The guidelines were result of a consensus approach of taking documentary evidence from the prescribed texts in addition to suggestions from a team of experienced clinicians. The consensus approach recommended consumption of spices to build body's immune system. Further, it also recommended application of oils to prevent entry of virus or bacteria into the nose (Table 1). An article recommending diet during the COVID-19 pandemic has been published recently.[2]Spices, especially turmeric and its alkaloids were found to act as anti-viral agents to inhibit Influenza Type-A, Hepatitis A, Zika, HIV, H5N1, hepatitis B, Hepatitis C, chikungunya anddengue.[3]

Spices include volatile oils/essential oils like cardamom oil; oleoresins like turmeric oil; alkaloids like capsaicin, piperine; saponins like trigonellenine; colorants like crocin, carotene and odd flavors like asafetida (Table 2).In parts of Asia, South-east Asia and in particular India, due to diverse cultural background different spices are used in different seasons in different foods and different types of cooking. For e.g. one of the widely used spices, turmeric offers plethora of benefits so much so that it is now used to treat cancer, chemoprevention, protecting elderly from Alzheimer's disease.

We believe that the consumption of spices everyday as part of diet (mixed in hot water, ghee, oil, milk or direct) offers significant protection by providing immunity. The list of commonly available spices along with the major constituents is available (Table 2).Due to COVID-19 pandemic and subsequent lockdown, Government promoted and partially funded researchers on generation of human safety and efficacy data on a number of products containing spice ingredients and spices. Having found evidence on potential role of spices in offering immunity to fight various diseases, we aimed at reviewing published scientific literature. Few publications have directly linked consumption of turmeric to control of COVID-19.[4]Yet another report correlated nations with higher consumption of per capita had lower number of COVID-19 cases per million.[5]We have also listed a number of human clinical trials that are being conducted on COVID-19 front line warriors using spices as ingredients. Spices were found to possess activities to regulate inflammation processes and inhibit abnormal cytokine release. Furthermore,

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Table 1: Consensus approach recommended for consumption of spices to boost immunity with special reference to respiratory health by the Ministry of AYUSH, Government of India during COVID-19 pandemic based on Indian system of medicine and traditional foods (AYUSH 2020).

Sl No	Spice/ ingredients
1	Spices like turmeric, cumin, coriander and garlic to be used in cooking
2	Herbal decoction made from basil leaves, cinnamon bark, black pepper, dry ginger and raisins mixed with jiggery and fresh lemon juice to be consumed as warm/hot tea twice a day.
3	Half tea spoon turmeric powder in hot milk called golden milk
4	Nasal application of sesame oil or coconut oil or ghee
5	Steam inhalation of fresh mint leaves or caraway seeds once in a day to treat dry cough and sore throat
6	Clove powder mixed with honey to be consumed twice or thrice in a day in case of throat irritation and cough

Table 2: List of important spices and their major constituents.

Sl No	Name of the spice	Major constituents
1	Asafoetida	AsacoumarinB,farnesferol A-C,
2	Capsicum	Capsaicinoids, flavonoids, capsanthin and natural colors
3	Cardamom	1,8-cineole, α-terpinyl acetate, α-terpinyl acetate, 1-8 cineole, limonene and linalool
4	Cinnamon	Cinnamaldehyde, eugenol, O-methoxycinnamaldehyde and monoterpenoids
5	Coriander	D-linalool, neryl acetate, γ-terpinene, camphor, α-pinene and geranyl acetate
6	Turmeric	Turmerone, ar-turmerone and zingiberene, curcuminoids
7	Cuminum	Flavonoid glycosides, tannin. Essential oil contains cuminic aldehyde, β-pinene, triterpene, p-cymene, β-farnesene
8	Fenugreek	fFavonoids, trigonelline, choline, gentianine and saponins. Essential oil contains β-pinene, camphor, β-caryophyllene and nerylacetate
9	Ginger	Zingiberene, ar-curcumene, gingerols, shogaols and zingerone.
10	Mustard	Allyl isothiocyanate
11	Black pepper	α-pinene, β-pinene, β-caryophyllene, limonene, piperine, brachymide B. Quercetin, isoquercetin, isorhamnetin, kaempferol

spices have shown antioxidant activity superior or equivalent to ascorbic acid. Based on the outcome we have arrived at reasonable conclusion that consumption of spices can provide innate and adaptive immunity in fighting various diseases including COVID-19.

We have searched Google, Google Scholar, PubMed, SciELO, Cochrane, Science Direct, Clinical Trial Registry, India (CTRI). Our search was limited to finding role of spices in offering anti-inflammatory activity, immunomodulation and anti-oxidant protection.

It is mandatory that all human clinical studies including herbal medicines, traditional medicines, pharmaceuticals and biopharmaceuticals have to register with CTRI, Indian Council of Medical Research, Government of India. For the purpose of the current study we have accessed CTRI website and collected various clinical studies registered for testing on common asymptomatic persons, front line workers either as protective, prophylactic or as add-on. We have shortlisted those clinical studies that were having products with one or more spices as ingredient. Table 3 summarizes clinical trials registered to undertake human studies containing one or spices as ingredients. Traditional remedies and Ayurvedic remedies are licensed under Drugs and Cosmetic Act(DCA-1940) and Rules, 1940 in India which are revised from time to time under the supervision of apex body.

COVID-19 and immunity

Immunity is defined as the body's ability to detect and resist a number of invading pathogens, infections enabling the body to prevent or resist disease, inhibit organ or tissue damage. Immunomodulators are biological or chemical molecules or substances that can stimulate, suppress or modulate either innate or adaptive immunity or both by offering immunity against pathogens.

World is now facing uncontrolled pandemic with the outbreak of new Corona virus (SARS-CoV-2) infection infecting millions of people all over the world.[6]Clinicians categorized COVID-19 patients into three stages, viz. stage-I, an asymptomatic incubation period; stage-II, non-severe symptomatic period with the presence of virus and stage-III, severe respiratory-symptomatic stage with high viral load.[6]Defense against viral infection is offered by body's innate and adaptive immunity. Effective anti-viral responses of host's innate and adaptive immunity including production of proinflammatory cytokines, the activation of T-cells, CD4+ and CD8+ and T-cells are essential for controlling viral replication and inflammation.[7]In COVID-19 patients, count of neutrophils and leukocytes increase whereas the total count of lymphocytes CD4+ T cells, CD8+ T cells, regulatory T cells, memory T cells, natural killer cells and B cells decrease. The unusual pro-inflammatory cytokine production is observed in patients with severe symptoms leading to acute respiratory distress syndrome (ARDS). Currently there are no treatments available but existing anti-viral therapies and other immunomodulatory and immunosuppressive treatments are used on case to case basis. Immunomodulatory therapies such as(interleukin)IL-6 antagonists, granulocyte colony stimulating factor (GM-CSF) inhibitors, IL-1 antagonists, IL-17 antagonists and anti-tumor necrosis factor (TNF) agents might be used for abnormal cytokine production and limit inflammational tissue damage.[7]We have provided here fundamental information on immunity and existing therapies to treat COVID-19. However, reviewing COVID-19 disease in detail is out of the scope of this article. Readers are requested to consult relevant topics for advanced knowledge on the same.

Spices and their role in offering immunity- Review of literature

Capsicum (*Capsicum annuum L.*): Capsicum is one of the important spices used widely in diet. It improves the flavor and taste by adding pungency to the preparations. The pungency is due to presence of an alkaloid called capsaicin in chili pepper fruit. Parts of Capsicum used as spice are; fruit powder, whole fresh fruit and dry fruit and in isolated form phenolics, flavonoids, capsaicinoids, natural colors, oleoresin and essential oils are used. Capsicum not only adds taste and improves color but also masks unwanted smell characteristic of meat and fish products. Like asafoetida, capsicum has carminative property. It also aids in improving digestion and bio-availability in the gut. Components of red

Table 3: List of Clinical trials registered with CTRI, ICMR as on 15th July 2020. Clinical trials were tabulated based on Spices as one of the main ingredient or Ayurvedic formulations that are under human clinical trials for immunity and treatment for COVI-19.

CTRI Number (Clinical Trial Number)	Title	Health condition	Intervention Name/ Product	Location
CTRI/2020/06/025801	Role of Herbal Imunomodulators in mild COVID-19 confirmed cases	Corona virus as the cause of diseases classified elsewhere	Tab. Bresol (contains *Curcuma longa, Cinnamomum zeylanicum*, *Ocimumsanctum,Elettaria cardamomum Cinnamomum tamala* and few other medicinal herbs)	Bangalore Medical college and research institute, Karnataka, India
CTRI/2020/05/025273	Impact of effect of Ayurvedic treatment on novel Corona virus disease	Respiratory failure, unspecified	Ayurvedic treatment	National Institute of Medical Sciences, Rajasthan, India
CTRI/2020/05/025430	Effect of ayurveda immunomodulator Drugs on health of corona warriors	Healthy personnel's engaged in care of covid-19 infected/ suspected persons	Decoction (contains *Piper longum* fruit and *Tinospora cordifolia* stem)	Dr S R Rajasthan Ayurved University, Rajasthan, India
CTRI/2020/05/024981	Clinical study on Dabur Chyawanprash as a preventive remedy in pandemic of COVID-19.	Immunity in Healthy Individuals	Dabur Chyawanprash (traditional product with winter cherry and ten other spices as ingredients)	Multiple locations
CTRI/2020/06/025592	Use of Herbal Medicine likeTulasi,Amruth(Giloy), Turmeric,Ashwagandha as add on treatment in COVID-19 Patients	Coronavirus as the cause of diseases classified elsewhere	Immunity Kit (contains turmeric and other medicinal herbs)	Bangalore Medical college and research institute, Karnataka, India
CTRI/2020/05/025434	A clinical trial to evaluate the Medicinal effects of ZingiVir-H as Anti-Viral therapy in COVID-19 patients	Coronavirus as the cause of diseases classified elsewhere	Zingivir-H (Ginger is ingredient)	Multiple locations
CTRI/2020/05/025317	Survey of mouth-dissolving turmeric lozenges in healthcare workers	Healthcare team serving duties at COVID-19 wards	Turmgel mouth dissolving lozenge 100 mg (Turmeric as ingredient)	KJ Somaiya Medical College and Hospital, Maharashtr, India
CTRI/2020/05/025156	Effect of Ayurveda intervention AYUSH-64 add-on therapy for patients with COVID-19 infection (Stage I)	Coronavirus as the cause of diseases classified elsewhere	Group I: Ayurveda intervention AYUSH-64 as add-on to standard treatment	Government Medical College, Nagpur, Maharashtra, India
CTRI/2020/07/026371	KabasuraKudineer, Shakti drops andTurmeric plus in the management of COVID-19	Coronavirus as thecause of diseases classified elsewhere	1.Shakti Drops (Nasal administration) 2.Turmeric plus tablets (Turmeric as an ingredient)	Mazumder Shaw Medical Centre, Narayana Hrudayalaya, Bangalore, Karnataka, India

Abbreviations: CTRI, The *Clinical Trials Registry- India; ICMR, Indian Council of Medical Research. List is representative and not exhaustive.*

pepper total phenolics, capsanthin, beta-carotene have been shown to prevent oxidation of cholesterol during heating.[8]Several reports on role of capsicum extracts and alkaloids on immunomodulation have been published. Takono *et al*.[9]reported that capsicum extract and capsaicin suppressed IL-2, interferon-γ, IL-4 and IL-5 production and reduction in CD3 cells and increase in CD-19 cells. It was found that capsicum extract modulate T-cell immune response via vanilloid receptor subfamily of TRP ion channels (TRPV1)-dependent and independent pathway.[9,10]Capsaicin promoted (Dendritic cells) DC activation and it counteracted the immune suppression.[11] In a study conducted on Jurkat T-cells (human leukemic T-cell line), capsaicin suppressed both T-cell receptor dependent and T-cell receptor independent production of IL-2.[12]Anti-inflammatory activities of pepper are also well documented. Bell pepper leaf extracts inhibited inflammatory cytokine production, inhibited cell proliferation without producing cytotoxicity and suppressed the expression of inflammatory proteins.[13]Similarly red pepper fruit showed anti-inflammatory activity via nitric oxide (NO) scavenging activity.[14] Likewise, green pepper showed lipooxygenase (LOX)inhibition followed by yellow and red pepper.[15]Sanchez *et al*.[16]reported that capsaicin inhibited early and late events in T-cell activation.

Several *in-vivo* studies were carried out to support immunomodulatory activity of capsicum extracts and its metabolites. On Wistar rats,[17] showed marked inhibition of natural killer (NK) cell and antibody dependent cytotoxic function. Santoni*etal*.[18]also demonstrated strong correlation between inhibition of cell proliferation and decreased numbers of CD5+ and CD4. On Wistar rats, capsicum extracts suppressed IL-2, interferon-γ, IL-4 or IL-5 production. Beltran *et al*.[10] showed capsaicin-elicited immunity is T cell-mediated process. Jang *et al*.[19] demonstrated that capsicum extracts significantly reduced ovalbumin-induced allergic airway inflammation. Hernandez-Ortega *et al*.[20]studied anti-inflammatory activity in mice. It was found that Guajillo pepper carotenoid extract significantly inhibited oedema formation and progress. Potential of immunomodulatory activity was studied in neonatal and adult rats by Nilsson andAhlstedt.[21] They found significant decrease in lymphocyte proliferative response to suboptimal concentrations of concanavalin A(ConA). In studies conducted on BALB/c mice, capsaicin was found to increase serum immunoglobulin concentrations (IgG and IgM).[22]

Cardamom (Elettaria cardamomum L.): Cardamom flavor is one of the pleasant among the spices. It has aromatic odor and slightly pungent taste. Important parts of economic use are cardamom essential oil, metabolites and oleoresins. As a spice it is used directly or powdered. Major constituents of volatile oil are 1,8-cineole and α-terpinyl acetate. Seed oil has α-terpinyl acetate, 1-8 cineole, limonene and linalool. Like asafoetida and capsicum, cardamom is used as carminative. But in Ayurveda cardamom is offered as a remedy for digestive problems. In addition, cardamom has many other pharmacological activities. It is used as an antioxidant, anti-inflammatory and immunomodulatory agent. We will review some of these activities below. Aqueous extract of cardamom was found to have immunomodulatory role.[23]Regular consumption of tea fortified with cardamom was shown to enhance

NK cell activity which is part of early innate immune response to infections.[24] Aqueous extracts of cardamom also provided protective effects on colon carcinogenesis induced *in vitro*.[25]Aqueous extracts were shown to enhance the level of detoxifying enzyme with decrease in lipid peroxidation levels.[26]

The essential oil had significant antioxidant activity.[27]Methanol extracts have protective ability against proxy nitrite mediated biomolecular damage.[28] Spice mixture containing cardamom reduced the levels of peroxidation markers in tissues and improved antioxidant status in male Wistar rats.[29]Cardamom showed 2,2-diphenyl-l-picrylhydrazyl(DPPH) radical scavenging activity.[30] Several *in vitro* based experiments were conducted to study various pharmacological activities of cardamom. Nair *et al*.[31]have concluded that cardamom has moderate levels of natural antioxidant properties due to presence of phenolics such as quercetin, kaempferol. Essential oils of cardamom also act as an antioxidant and helps in scavenging free radicals.[32,33]*In vivo* studies using Sprague Dawley rats, Raksamiharja *et al*.[34] showed that distillate of cardamom increases the amount of lymphocyte, white blood, CD4+ and CD8+ cells and has potential to develop into immunostimulating agent. In another study Al-Zuhair *et al*.[35] showed oil extract of cardamom reduced inflammation in carrageenan induced rat paw oedema.

Cinnamon (Cinnamomum zeylanicum Garcin ex Blume*)*: Cinnamon as a spice is known since Biblical times and is one of the oldest known spices. Similar to cardamom, cinnamon is sweet spice with pleasant aroma and taste. Cinnamon bark, essential oil and oleoresins have proven medicinal uses since olden times. Important constituents of cinnamon are cinnamaldehyde, eugenol, O-methoxycinnamaldehyde and monoterpenoids. It is traditionally used to treat flatulence, loss of appetite and as a carminative. However, cinnamon has anti-oxidant, anti-inflammatory and immunomodulatory roles in addition to many other benefits.[36] The methanolic extract has an excellent NO-scavenging ability through the mechanism of inhibition of iNOS expression.[37]Cinnamol polyphenol extract was found to reduce OGD induced cell swelling.[38]Treatment with cinnamon extract inhibited maturation of MHC II (+)(Major Histocompatibility Complex) APCs or CD11C (+) dendritic cells by suppressing expression of cylcooxygenase-2 (COX-2) and MHC II. Cinnamon extract also induced dendritic cells that produce low levels of proinflammatory cytokines IL-1β, IL-6, IL-12, IFN-γ and TNF-α while expressing high levels of immunoregulatory cytokines. These results suggested the potential of cinnamon extracts as a source of an anti-inflammatory cytokines.[23]The essential oil of cinnamon was shown to have antioxidant activity using in vitro models.[39] A concentrated water extract of cinnamon contained the maximum amount of phenolics and showed antioxidant activities.[40] Kim *et al*.[41] reported cinnamaldehyde to possess anti-inflammatory activities and a role in regulation of age-related metabolic pathways. Cinnamaldehyde inhibited the activation of NF-κB via three signal transduction pathways, NF-κB-inducing kinase/IκB kinase (NIK/IKK), ERK and p38 MAPK.

Several *in vitro* studies have been conducted to identify and establish role of cinnamon and its metabolites in offering immunomodulation. *C. zeylanicum* aqueous extract significantly induced thymic cells lymphoproliferation. Further, spice aqueous extracts significantly reduce up to 100% nitric oxide production by LPS-stimulated macrophages.[42] Ethanolic extract suppressed *P.acnes* stimulated NF-κB mediated TNF-α, IL-1B and IL-8 production.[43] Water extract also inhibited anti-CD3 Ab-stimulated IFN-γ and IL-4 at the mRNA and secreted protein level.[44] Extract has inhibitory effect on LPS-induced activity of NF-κB.

Main constituents of cinnamon, eugenol and cinnamaldehyde have promoted anti-inflammatory activity.[45] Gruenwald*et al*.[46] has shown that above compounds of cinnamon inhibited COX-2 enzymes. 2-hydroxycinnamaldehyde inhibited LP stimulated NO production and NF-κB activation via redox-related NF-κB/IKK and mitogen activated MAPK pathway through reduction of oxidative stress.[41]

In-vivo studies related to role of cinnamon have been studied. In immune-compromised mice, bark extracts of cinnamon have improved humoral, cellular and innate response of immune system.[47] Low dose of cinnamon produced an increase in serum immunoglobulin's and high dose decreased *Pasteurella muttocida* induced mortality by 17%; increased the phagocytic index in carbon clearance test, increased neutrophil adhesion, increased serum immunoglobulin levels and antibody titer values.[48] There is one clinical trial conducted on human subjects in double-blind, placebo controlled design on 34 female breast cancer patients to study cinnamon's role as chemo-preventive agent. Cinnamon bark extract showed significant protection from chemotherapy –induced severe weight loss and alopecia.[49]

Coriander (*Coriandrum sativum L.*)*:* Coriander is also an oldest known spice in the history. Coriander is a popular flavor used to flavor almost every cooking due to its characteristic aroma. Coriander fresh leaves are most widely used plant part. However, dried seeds are also used in special spice mixtures. In addition, coriander's alkaloids, essential oils and oleoresins have important pharmacological importance. The major constituents of oil are D-linalool, neryl acetate, γ-terpinene, camphor, α-pinene and geranyl acetate.[23] Major constituents of seed and fresh leaves are tocopherols, carotenoids, phenolics, flavanols and anthocyanins. Coriander is carminative, stomachic, spasmolytic and antibacterial. Essential oil is having excellent anti-bacterial, anti-fungal and anti-microbial activity. Furthermore, coriander has proven antioxidant activity. It is an effective antioxidant showing DPPH radical scavenging activity, lipoxygenase inhibition, phospholipid peroxidation inhibition, hydroxyl radical scavenging activity, SOD activity and anti-lipid peroxidation. Ethanolic, methanolic, chloroform, ethylacetate and water extracts were found to have high total phenolic content.[50]Sreelatha *et al*.[51] reported protection of liver from oxidative stress induced by CCl_4. The aqueous extract has superior antioxidant activity equivalent to ascorbic acid.[52]Extracts also have anti-inflammatory activity which inhibits proinflammatory mediator expression by suppressing NF-κB activation and MAPK signal transduction pathway in LPS induced macrophages.[53] Hot water extract has high antioxidant activity owing to presence of phenolics and flavonoids.[54] The ethanolic extract has hepatoprotective activity which might be due to antioxidant potential of phenolics.[55]

Few *in vitro* studies have been conducted on coriander extracts. Aqueous and methanolic extract caused significant L5178Y- R lymphoma cell toxicity showing anti-tumor activity.[42]The aqueous crude extracts stimulated the proliferation of human peripheral blood mononuclear cells (PBMC) and the secretion of IFN-γ.[56,57]Methanolic extracts exhibited remarkable DPPH radical scavenging activity due to the presence of rich antioxidants.[58] Methanolic extracts showed better antioxidant activity than ethanolic extract and the DPPH radical scavenging ability of methanolic extract was higher than that of BHT.[59,60]Al Mofleh *et al*.[61]compared the activities between leaf and seed extracts. Upon comparison it was found that leaf ethyl acetate extract showed most potent DPPH radical scavenging activity. Singletary 2016 showed that coriander extract reduced hepatic damage, liver oxidative damage and brain oxidative stress and at the same time activity of antioxidant enzymes increased thereby showing correlation between protection against oxidative damage and antioxidant enzymes. *In vivo* studies conducted on rats showed that the extract inhibited 40.81% oedema after third hour of treatment at 200 mg/g dose.[62]

A study on role of coriander on human (ultraviolet erythrema test) was carried out by Reuter *et al*.[63] The lipolotion with 0.5% coriander

essential oil reduced significantly the UV-induced erythrema. It was also found that extract was well tolerated.

Turmeric (*Curcuma longa* L.)*:*Turmeric is one of the most commonly and widely used spices. Rhizome is plant part of importance. Dried rhizome is used after powdering in several food preparations. Mixed in hot milk if consumed, the golden milk offers immunity (Table 1). Turmeric powder is applied on face as paste to control acne formation. In some traditional homes, turmeric and neem leaves are mixed and boiled. This mixture is given as bath to convalescing patients recovering from skin diseases, bacterial and viral diseases. Therefore, turmeric is a household remedy. Recently a Chinese group investigated the antiviral properties of curcumin against Transmissible gastroenteritis virus (TGEV). It was demonstrated that curcumin strongly inhibited TGEV proliferation and viral protein expression in a dose-dependent manner. They also observed that curcumin exhibited direct virucidal abilities in a dose-, temperature- and time-dependent manner. Mode of action was that curcumin acted in early phase of TGEV replication. The group also suggested that curcumin might be a candidate drug for effective control of TGEV infection.[64]

Turmeric is one among few clinically proven prominent immunomodulatory spice.[65]Turmeric contains an essential oil, oleoresin, alkaloids and isolated compounds such as curcuminoids. Essential oil is composed of sesquiterpenes. The alkaloids responsible for aroma are turmerone, ar-turmerone and zingiberene. The active constituents of turmeric are curcuminoids and volatile oils including tumerone, atlantone and zingiberone. Yellow color of turmeric is due to presence of curcumonoids, the polyphenols. Major curcuminoids are curcumin, demethoxycurcumin, bisdemethoxycurcumin.[66,67]Pure curcumin is insoluble in water. The bioavailability of oral curcumin is low because upto 65% of curcumin passes through GI tract. Absorbed curcumin is metabolized in intestine and liver.

Turmeric and its constituents are having a range of antioxidant activity such as capability to scavenge the primary radicals, repair and construction of lipid membrane aided by glutathione peroxidase. Churchill *et al*.[68] studied the effect of curcumin on lymphocytes and found an increase in mucosal CD4(+) T-cells and B-cells in animals. Ramos *et al*.[69]demonstrated that turmeric displayed IC_{50} of <30 µg/ml in the DPPH assay and IC_{50} of <32 µg/ml in lipid peroxidation inhibition testing. The methanolic extract showed peroxynitrile scavenging activity with IC_{50} 17 µg/ml.[70]Bosca*et al*.[71] showed a 45 days intake of hydroalcoholic extract of turmeric which resulted in decrease in the levels of serum lipid peroxides, which has a role in senescence and atherosclerosis.

Turmeric is having potential anti-inflammatory activity. Due to its anti-inflammatory activity, turmeric is widely used in treating osteoarthritis. It has been found to block the production of certain prostaglandins and also have effects similar to cortisone and non-steroidal anti- inflammatory drugs. Atkinson and Hunter[72]reported the effect of turmeric extract in the treatment of steroid-dependent inflammatory bowel disease. The inhibitors of prostaglandin biosynthesis and NO production are potential anti-inflammatory and anti-cancer candidates.[73]It was found that methanolic extracts inhibited prostaglandin E-2 production and NO formation towards inhibition of COX-2 and iNOS, respectively in mouse macrophages RAW264.7 cells.

Isolated compounds from turmeric such as curcumin is known to have anti-bacterial, anti-inflammatory, anti-cancer, anti-arthritic, hepatoprotective, anti hypercholesterolemic, chemoprotective and immunomodulatory activities. Another compound of turmeric, curcuminoids are also known to have several beneficial properties similar to curcumin. However, in this article we will summarize only immunomodulatory and anti-inflammatory functions. Curcuminoids are able to inhibit LPS induced production of TNF-α, IL-1β and the activation of NF-κB in human monocyte derived cells.[74] Protease activated receptors (PARs) play a vital role in inflammation. Human leukemic mast cells (HMC1) co-express PAR2 and PAR4. A number of molecules involved in inflammation were inhibited by curcumin including phospholipases, lipoxygenase, COX 2, thrombaxane, prostaglandins, NO, TNF, IL-12.[75] The cytokine macrophage migration inhibitory factor is crucial factor in the pathogenesis of rheumatoid arthritis.[76] Curcumin was found to be most potent inhibitor. The development of cell mediated immune response involves a complex network of cytokine signals generated by APCs or T helper (Th1 and Th 2) cells. Activated monocytes/macrophages release proinflammatory cytokines such as TNF-α, IL-1 and IL-6 that play a role in immunity response.[67] Th1 cells secrete IL-2 and IFN-γ which promote cell mediated immunity. Th2 cells secrete IL-4, IL-5, IL-6 and transforming growth factor (TGF-β) that regulate humoral immunity. And negatively regulate cell mediated immunity. Curcumin inhibited TNF-α at a higher concentration.[77]Kang *et al*.[78] showed the inhibition of IL-12 production of murine macrophages stimulated with LPS. Macrophages treated with curcumin reduced the ability of antigen primed CD 4+ T-cells to produce IFN-α but increased the production of IL-4. Gao *et al*.[79]showed that curcumin irreversibly inhibited expression of IL-2, IFN-γ by mitogen stimulated splenic T-cells and IL-12 production in peritoneal macrophages. Curcumin inhibited proinflammatory IL-1β, IL-6 and TNF-α by bone marrow derived DCs stimulated with LPS and demonstrated that translocation of NF-κB by curcumin was responsible for impairment of cytokine production.[80]Srimal and Dhawan[81] showed that curcumin is as potent as phenylbutazone in the carrageenan induced oedema test in the rats. Activated monocytes and macrophages release proinflammatory cytokines TNF, IL-1, IFN to induce inflammation. The process of inflammation involve production of prostaglandins, thromboxanes and leukotrienes-known as eicosanoids by macrophages and neutrophils. They are synthesized through arachidonic acid (AA) by COX2 or lipoxygenase (LOX). COX 2 is induced by inflammatory insult by cells. AA derived compounds are responsible to pain, inflammation, swelling and thrombosis. Hong *et al*.[82] showed inhibition of AA generation by curcumin. Huang *et al*.[83] also showed inhibition of AA *in vitro*, but the mechanism of inhibition is by both LOX and COX. Flynn *et al*.[84] showed inhibition of 5-HETE production by curcumin. Curcumin also was shown to inhibit the production of superoxide and NO by inflammatory cells thereby offering anti-inflammatory activity.[85]Curcumin has been shown to inhibit proinflammatory cytokines TNF, IL-1, IFN that play important role in anti-inflammatory activity. Curcumin's inhibitory effect on the NF-κB pathway is an example of its anti-inflammatory effect. It is shown to decrease metabolism of AA by downregulating the activity of lipoxygenase and COX 2 at transcriptional level.[86,87]Curcumin has been shown to possess activity similar to TNF blockers, vascular endothelial cell growth factor blocker, human epidermal growth factor receptor blockers and HER2 blocker.[88]Curcumin was found to prevent the reduction of cytochrome enzyme P450 expression induced in inflammatory conditions.[89]Curcumin was further found to modulate proinflammatory cytokines expression, attenuate IL-1β TNBS- induced damage and increase IL-10 expression.[90]Curcumin scavenges reactive oxygen species produced by macrophages (super oxide anions, H_2O_2 and nitrite radicals) both *in-vivo* and *in vitro* in a study conducted on rat peritoneal macrophages.[91]Curcumin also reduces the amount of reactive oxygen species generated in response to oxidative stress by downregulating iNOS activity in macrophages.[92] Curcumin treatment reduced NO generation and protection of neural cells from oxidative stress and thus indirectly benefitting neuroinflammation protection associated with Alzheimers.[93]Curcumin's free radical scavenging activity is responsible for anti-inflammatory properties. Pure curcuminoids I, II, III had strong antioxidant activity as determined by DPPH method.[94]A

polyherbal formulation containing curcumin as one of the ingredients was found to reduce levels lipid peroxidation and increased levels of antioxidative enzymes.[95] In summary, curcumin is shown to have effective DPPH scavenging, DMPD (+) scavenging, superoxide radical scavenging, hydrogen peroxide scavenging and ferrous $Fe^{(2+)}$ chelating activities.[96]Liu *et al*.[97] in a study conducted using bone marrow derived dendritic cells found that curcuma blocked STAT 3. Study on murine macrophage cells showed inhibition of IL-6, TNF-α, PTGS-2 and reduction of p38 MAPK and increase of SOCS1 and SOCS3.[98,99] BV-2 microglia cells treated with curcuma showed reduction in NF-κB, iNOS and IL-6, TNF-α, IL-1β levels.[100]Further, Cianciulli *et al*.[101] also reported reduction in iNOS, COX 2, HO-1, reduction in MAPK, NF-κB, TNF-α, NO, PGE-2 on same cells. Turmeric inhibited LPS induced IL-2, IL-1β, IL-6 and TNF-α and the phosphorylation of MAPK and NF-κB nuclear translocation.[80,102]

Studies conducted *in-vivo* on rats fed with dietary curcumin at 40 mg/kg, IgG levels were significantly increased after 5 weeks.[103]IgG molecules are antibodies produced initially upon infection of cell with pathogen. This shows that curcumin can induce IgG levels to fight against invading pathogen which explains its importance in imparting immunity. Cell mediated immunity in which antigen sensitized T-lymphocytes mediate the immune response against pathogens, rejection of organ transplants etc., Cell mediated immunity is measured by T-cell proliferation, production of cytokines and T cells. Effect of curcumin on human T-cell proliferation showed that curcumin inhibited the isopentenyl pyrophosphate induced proliferation of cells.[104]

Clinical trials: Curcumin has long history of safe use. However, first clinical study was conducted in the year 2001[105] with series of dosages, viz., 500 mg, 1000 mg, 2000 mg, 4000 mg and 8000 mg daily for 3 months on patients. The study identified no treatment related toxicity upto 8000 mg for 3 months.[106] In yet another study, curcuminoids were given at a dose of 450 mg. 900 mg, 1800 mg and 3600 mg per day upto 4 months on 15 patients with refractory colorectal cancer. The drug was found to be well tolerated.[107] Phase-I clinical studies confirmed the safety of curcumin in humans for a period of 4 months.[105] Phase-II studies were conducted mainly to evaluate curcumin on treating chronic inflammation, malignancies. But the studies were on small group of patients. In a study conducted on 18 patients with rheumatoid arthritis, it was found that 1200 mg/day curcumin showed improvement in rheumatoid symptoms.[108] Heng and colleagues[109] reported topical use of curcumin in the treatment of active plaque lesions. After 3-4 weeks, six of six curcumin treated plaques improved by 25-70%. Overall, turmeric and its metabolites have versatile biological activities in modulating immunity and anti-inflammation.

Fenugreek (*Trigonella foenum-graecum* L): Fenugreek is the ancient spice known since 4000 B.C. Fenugreek has spicy aroma, pungent bitter taste. Seeds are plant parts of economic importance. Essential oil and oleoresin is also obtained and are equally important. Seeds contain flavonoids, trigonelline, choline, gentianine and saponins. Essential oil contains β-pinene, camphor, β-caryophyllene and nerylacetate. Fenugreek's pharmacological importance has been well recognized. It is used to treat mouth ulcers, cancer. It is emollient, laxative and a vermifuge. Fenugreek is mainly used to treat diabetes[23] and to treat dandruff and promote hair growth. The anti-hyperglycemic compound purified from fenugreek seeds was found to decrease lipid content of liver.[110] Fenugreek and its active constituents could be useful in offering skin damage protection.[111] Further, fenugreek is known to have strong antioxidant properties.[112-114] Phenolics are known to have antioxidant properties which prevent lipid peroxidation.[115] Aqueous extracts have normalized the levels in lipid peroxidation, oxidative stress in the liver, kidney.[116] Kaviarasan *et al*.[117] reported reduced levels of lipid peroxidation and increased activities of anti-oxidant enzymes in rats. An aqueous extract of germinated fenugreek extract has highest antioxidant activity, radical scavenging and inhibition of lipid peroxidation in mitochondrial preparation of rat liver.[118] Fenugreek leaf powder supplementation greatly reduced oxidative stress in streptozotocin-induced diabetic rats.[119]Lipid peroxidation was lowered and antioxidant enzymes activity was increased supporting fenugreek's antioxidant ability. Meera *et al*.[120] reported hepatoprotective activities by ethanolic extracts against liver damage. The extract was also found to be exhibiting significant activity in superoxide radicals and NO radical scavenging. Immunomodulatory effect was reported on Zucker obese (fa/fa) rats when aqueous extracts were fed for 10 days.[121] Aqueous extracts have also shown immunomodulatory effect on Swiss mice.[122] Fenugreek exhibited significantly high phagocytic index indicating stimulation of reticulo-endothelial system.[123] Methanolic extract showed significant increase in lymphocytes and T-cell rosette formation. Diabetic rats showed low activities of SOD, catalase, glutathione peroxidase and reduced glutathione in kidney which were restored to normal levels after treating with fenugreek oil.[124] Fenugreek extract elicited increase in phagocytic index and phagocytic capacity of macrophages indicating immunostimulatory effect in Swiss albino male mice.[122] The antioxidant property of fenugreek seeds might be contributing to protective effect on immunosuppressed mice, further, restoration of tissue antioxidant molecules by fenugreek extract was observed.

When rats were treated with fenugreek extract, inhibition of inflammation swelling was observed. [125,126] Petroleum ether extracts of fenugreek indicated that fenugreek reduced 85% inflammation of the paw in formaldehyde and carrageenan induced paw oedema.[127] Methanol extract inhibited production of phorbol-12-myristate-13-acetate induced inflammatory cytokines in cultured THP-1 cells.[111] In an adjuvant induced arthritis in albino rats, ethanol extract significantly decreased paw oedema and decreased levels of IL-1a, IL-1b, IL-2, IL-6 and TNF-α. The extract also reduced levels of LPO and increased SOD and GSH levels in cartilage tissue.[128] The extract showed significant analgesic and anti-inflammatory activity in carrageenan induced rat paw oedema as compared to diclofenac sodium. It was suggested that flavonoid component of extract has significant anti-inflammatory activity.[129]

Ginger (*Zingiber officinale* Roscoe): Ginger, like turmeric and chili pepper is very widely used spice in household. Ginger has warm, sweet, pungent and aromatic flavor. Rhizome is used fresh and dried ginger is used in spice mix. In addition to rhizome, essential oil and oleoresin are parts of medicinal importance. Major constituents of the essential oil are zingiberene and ar-curcumene. The pungent taste constituents are gingerols, shogaols and zingerone. One of the traditional uses of ginger is to treat dyspepsia and nausea, cough, stomach pain. In addition, ginger is known to have other health benefits such as antibacterial, antioxidant, anti-inflammatory, immunomodulatory, anti-ulcer, gastro protective, cholesterol lowering, antifungal.[23]Ginger reduces release of prostaglandin and thromboxane in lung parenchyma suggesting its role in anti-inflammatory activity.[130] Ginger inhibited NF-κB activation and diminished the secretion of vascular endothelial growth factor and IL-8. Ginger with its 12 important compounds provide antioxidant activity 40 times higher than Vit-E. Dugasani *et al*.[131] found that 6-shogaol has potent antioxidant and anti-inflammatory activity. Ginger alkaloid 10-gingerol is potent among gingerols. Ginger compounds protect lipid peroxidation in mouse liver hepatocytes.[132]Treatment of rats with 1% dietary ginger was found to increase the activity of SOD, catalase, GPx, GR and glutathione thus suggesting its protective role.[133]In another experiment, lindane administration enhanced lipid peroxidation and antioxidant defenses in male albino rats. But, ginger diet attenuated lipid peroxidation by modulating oxygen free radicals scavenging enzyme.[134]In ginger diet doxorubicin treated rat groups, antioxidant parameters malondialdehyde(MDA), glutathione (GSH) levels and

enzyme activities of glutathione S-transferase(GST), SOD, catalase, glutathione peroxidase(GPx)were restored normally compared to control groups.[135] Compounds isolated from ginger were found to significantly decrease lipopolysaccharide induced NO production and significantly reduced inducible NO synthase.[136] Hexane extract was found to have anti-inflammatory properties because it can suppress transcription of inflammatory mediator genes through the MAPK and NF-κB signaling pathways.[137]Ginger essential oil was studied for antioxidant activity. It exhibited strong antioxidant activity measured by DPPH of FRAP method. A component of ginger, (6)-paradol has chemoprotective and lipid peroxidation and antioxidant activity.[138] Furthermore, (6)-gingerol exhibited preventive potential for the management of Alzheimer's disease through antioxidant activity.[139]Ginger also exhibited neuroprotective effect by accelerating brain antioxidant defense mechanism.[140]

Several *in vitro* studies were reported on role of ginger and its metabolites in offering various pharmacological benefits. Stoilova *et al.*[141] reported (9)(6)-dehydroshogaol, (6) shogaol and 1-dehydro (6)-gingerdione having good inhibitors of NO synthase in activated macrophages. Ginger extract also shown to have inhibited DPPH upto 90%. Zingerone is effective scavenger of the free radicals like super oxide, peroxyl and peroxyl nitrite.[142] Topical application of 6-gingerol inhibited TPA induced COX 2 expression and suppressed NF-κB DNA binding activity in mice skin.[143]Essential oil and oleoresin were found to be better antioxidants than butylated hydroxyanisole.[144] Ginger is known to relieve pain in osteoarthritis patients mainly due to its anti-inflammatory activity.[145] Ginger, like turmeric is known to have activity similar to non-steroidal anti-inflammatory drugs (NSAIDs) because it suppresses prostaglandin synthesis through inhibition of COX 1and COX 2.[146] Ginger suppressed lymphocyte proliferation found in *in –vitro* study which was mediated by decrease in IL-2 and IL-10 production.[147] Ginger volatile oil significantly inhibited T-lymphocyte proliferation, decrease in the number of total lymphocytes and T-helper cells. It also inhibited IL-1 and secretion of the mice peritoneal macrophage.[148]

Several *in-vivo* studies were reported using ginger extracts to demonstrate its anti-inflammatory and immunomodulatory roles. A study conducted on 12-*O*-tetradecanoyl phorbol-13-acetate(TPA)-treated female ICR mice and rats of the effect of 6-gingerol and 6-paradol, it was shown that ginger alkaloids have anti-inflammatory activity and suppressed the TNF-α production.[143] Ginger extract significantly reduced elevated expression of NF-κB and TNF-α in rats with liver cancer. Ginger may act as an anti-cancer and anti-inflammatory agent by inactivating NF-κB through the suppression of pro-inflammatory TNF-α (Habib2008). Essential oil showed to exert anti-inflammatory effect by preventing alterations of some cytokines/ inflammatory biomarkers – IL-6, IL-10 and TNF-α.[149] Improved humoral immunity was found in mice fed with 50% ethanolic ginger extract for seven days.[150]Volatile oil may influence both cell mediated immune response and non-specific proliferation of T-lymphocyte.[148] Essential oil suppressed chronic inflammation induced by formalin in kinin, carrageenan induced paw oedema and chronic oedema.[151] It even inhibited chronic joint inflammation without any effects in initial acute phase of joint inflammation or granuloma formation at the site of Streptococcal cell wall deposition in liver.[152]

Human studies were carried out to evaluate ginger and its metabolites role. In a randomized double-blind placebo controlled study it was found that ginger can improve rheumatoid arthritis by decreasing disease manifestations via increasing Fox P3 genes expression and by decreasing RORyt and T-bet gene expression.[153]In another study involving 25 patients, hydroalcoholic extract was shown to reduce expression of GATA-3, ROR-yt and T-bet in PBMCs of asthmatic patients.[154]

Black pepper (Piper nigrum L): Black pepper is an aromatic and pungent spice whose pungency differs from that of capsaicin. It also adds different flavor and taste. Pepper seeds are important parts of commercial use. Essential oil and oleoresin are obtained from seeds. Seeds contain alkaloid called piperine. The essential oil contains α-pinene, β-pinene, β-caryophyllene, limonene as major constituents. The major alkaloids are piperine, brachymide B and others. Quercetin, isoquercetin, isorhamnetin, kaempferol are major flavanols found in pepper. Pepper is mainly used to stimulate taste buds, improve digestion and treating flatulence. Further, it is also having carminative property, antibacterial, antioxidant, anti-inflammatory and immunomodulatory activity.[23]Important alkaloid, piperine has been shown to increase bioavailability. In a separate experiment, it was demonstrated that bioavailability of epigallo catechin-3-gallate (EGCG), a phenolic component of tea has improved when taken with piperine in mice.[155]Piperine inhibits LPS induced endotoxin shock through inhibition of type I IFN production.[156] It lowers lipid peroxidation *in vivo* and protects against oxidative damage by quenching free radicals and ROS. Piperine was shown to protect the plasmid DNA from degradation by gamma-radiation.[157] Supplementation of diet with piperine in male Wistar rats lowered conjugated dienes and thiobarbituric acid reactive substances (TBARS) and maintained the levels of reduced glutathione (GSH) and antioxidative enzymes SOD, catalase, GPx, GST-indicating its role as an antioxidant. It was also found that supplementation of high fat diet with piperine protected erythrocytes from oxidative stress by improving antioxidant status in male Wistar rats.[158] Different fractions of petroleum ether extracts of pepper have strong antioxidant activity.[159] Essential oil and oleoresins also showed strong antioxidant capacity in comparison to BHA and BHT.[160] Black pepper extracts inhibited by LPO by 45-85%, COX enzymes by 31-80% and cancer cell proliferation by 3.5-86.8%.[161]

Several *in-vitro* and *in-vivo* studies have been conducted in support of pepper's pharmacological activities. Pepper aqueous extract reduce up to 100% NO production by LPS-stimulated macrophages.[39] Ethanol seed extract enhanced the proliferation of macrophage cell line J774a-1.[16] [2]Piperine has exhibited anti-inflammatory activity. It reduced synthesis of prostaglandin E_2on IL-1β stimulated fibroblast like synoviocytes.[163] Piperine treated mouse splenocytes exhibited an increase in the secretion of Th-1 cytokines (IFN-γ and IL-2), increased macrophage activation and proliferation of T- and B- cell.[164]Piperine inhibited B-cell proliferation by causing GO/G1 phase cell cycle arrest and inhibited immunoglobulin's in mouse B cells.[165] Piperine inhibited polyclonal antigen specific T-lymphocyte proliferation without affecting cell viability. Piperine also suppressed T-lymphocyte entry into the S and G2/M phase of cell cycle.[166] Aqueous extracts enhanced splenocyte proliferation in experiments conducted on BALB/c and C57/BL6 mice. ELISA results revealed that pepper extracts significantly enhanced T-helper (Th1) cytokine release by splenocytes signifying its immunomodulatory activity.[167] Piperine showed anti-inflammatory activity in rats. It acted partially through stimulation of pituitary adrenal axis. Oxidative stress and apoptotic markers altered by cadmium toxicity were modulated by piperine in BALB/c mice. Inhibition of cell proliferative response, alterations in T-cell and B-cell phenotypes, cytokines released and morphological changes were stored to normalcy.[168]

Based on findings from *in vitro*, *in vivo* and to certain extent human studies scientific evidence is available on the potential role of spices in offering both innate and adaptive immunity in humans. It is interesting to note that all spices which we have reviewed demonstrated reasonable evidence in providing immunity, anti-inflammatory and anti-oxidant activity. However, we did not find many human clinical trials. Documented evidence on human clinical trials was available on spices such as turmeric, coriandrum, cinnamonand ginger. Several other spices and condiments are also regularly consumed, a non-exhaustive

list of them include- clove, sesame seeds(white and black), caraway seeds, bay leaves, white pepper, long pepper, star anise, Indian rose chestnut, fennel seeds, maceandcarom (bishop's weed).

Spices might offer protection against SARS-CoV-2 infection

Treatment for COVID-19 disease caused by SARS-Cov-2 is still uncertain. However, some of the anti-inflammatory treatments offered to rheumatology, existing anti-virals and antagonists for proinflammatory cytokinins are being considered (Table 4) as possible therapy in severe cases. Though, research efforts are under way world-wide to develop vaccine and treatment, it may be a while before they are available for treatment. It is now evident that COVID-19 has proximate association with innate and adaptive immune responses. The responses decline with age, nutrition and diseases. Roy *et al*.[3]found that curcuminoids and Zn, both considered as GRAS substances, identified as nutraceutical and nutrient, respectively have proven history of antiviral activity leading to release of prophylactic candidates against COVID-19. Curcumin, through inhibition of viral entry into cells, suppression of viral replication, modulation of cytokines, act as antiviral agent to inhibit Influenza Type A, Hepatitis A, Zika, HIV etc.[3,4]Roy *et al*.[3] conducted *in silico* studies and demonstrated that curcumin directly binds to receptor binding domain of viral spike proteins of SARS-CoV-2 virus to prevent virus entry. Further, in our assessment of published literature it was shown that curcumin inhibits release of abnormal cytokine storm aiding to control of COVID-19 progression. Manoharan *et al*.[4] proposed that Curcumin acts as an attenuator via modulating the proinflammatory effects of Angiotensin-II-AT1 receptor-signaling pathways to reduce respiratory distress. Jia *et al*.[169] demonstrated that an emulsion made of curcumin as a topical application can prevent the SARS-CoV-2 infection. Therefore, research points to role of turmeric and its metabolites in controlling entry of virus and at later stages controlling release of abnormal cytokine release. In yet another interesting study,[5]the authors have correlated data drawn from 163 countries during COVID-19 pandemic season. They have concluded that nations with higher consumption of spices have shown lesser COVID-19 cases and higher recovery rates compared to nations with lower spice consumption. Over 300 clinical trials have been reported on the beneficial effects of curcumin against various diseases such as Inflammatory diseases, neurological disorders, cardio-vascular diseases, pulmonary diseases, cancer and so on.[170]They have also reported suppression of pulmonary edema and fibrosin-associated pathways in COVID-19 infections. The evidences points to role of curcumin in controlling various diseases including COVID-19.

First line of defense against SARS-CoV-2 infection is the individual's innate immunity. Innate immunity is dependent on person's health and age in addition to nutrition status. Though exact treatment is not available but several options are proposed. We wish to discuss some of the proposed treatments:i) IL-6 antagonists: IL-6 acts as an inducer of proliferation and differentiation of immune cells. In COVID-19 patients, high levels of IL-6 were detected. IL-6 and Janus Kinase (JAK) inhibitors were thought to be involved in inhibition of proinflammatory cytokines involved in 'cytokine storm'. Thus, by inhibiting IL-6 or JAK inhibitors cytokine storm can be controlled; ii) TNF-α inhibitors: TNF-α is one of the most potent proinflammatory cytokines. Levels of TNF-α were found to be in elevated levels in serum of COVID-19 patients. TNF-α is involved in viral entry into host cell.[7]It is hypothesized that TNF- inhibitors may be effective in blocking viral entry and detrimental effects of TNF-α; iii) IL-17 blocker: IL-17 is one of the cytokines found abundantly in severe COVID-19 patients. IL-17 is associated with severe lung inflammation and thus damages to tissue. Blocking IL-17 may be an effective treatment to reduce organ damage; iv) some of the NSAIDs reported to have direct antiviral effect on SARS-CoV-2 by interfering with viral RNA synthesis. Though, evidence is weak, NSAIDs such as indomethacin are being proposed in the treatment.

Upon infection immunoglobulin IgM is detected in patient's blood in 3-6 days and IgG after 8 days.[171]It was found that levels of IgM and IgG progressively increased from day 7 to day 20. Researchers also showed that 7-9 days after onset of symptoms, high concentrations of T helper cells (Th), NK and B cells were detected and it was concluded that early adaptive immune system may be related to better clinical outcome.

As we conclude from studies conducted on spices, scientific evidence is mounting on the role of spices such as capsicum, ginger, turmeric, black pepper and cinnamon bark in offering effective immunity. Capsicum found to have increased serum immunoglobulin concentrations (IgM and IgG). Almost all spices reviewed in the present report have inhibited proinflammatory cytokines, thus may be helping to reduce/limit 'cytokine storm'. Spices like curcuma showed reduction in NF-κB, IL-6[98] inhibited TNF-α, IL-1β and the activation of NF-κB in human monocyte derived cells.[74]Curcumin essential oil inhibited NO synthase, IL-1 and IL-6, COX-2 thus showing evidence of curcumin's anti-inflammatory role. Turmeric was shown to inhibit a number

Table 4: Potential anti-inflammatory treatments currently available for COVID-19.[7]

Sl No	Treatment	Proposed mode of action	Reference
1	Corticosteroids	Corticosteroids are more likely to function on inflammation-mediated lung injury and interstitial fibrosis at late-stage of Acute Respiratory Distress Syndrome	[172]
2	Chloroquine and hydroxychloroquine	By blocking the virus-receptor binding and virus-endosome fusion; By increasing the activity of Treg	[7]
3	CQ, HCQ and intravenous immunoglobulin (IVIg)	By inhibitingthe production of cytokines in macrophages and the antigen presentation in dendritic cells	[7]
4	Intravenous immunoglobulin (IVIg)- IVIg is a blood product containing polyclonal immunoglobulin G	One of the proposed mechanisms is the interaction of IgG-Fc with Fc gamma receptors located on immune cells, resulting in pleiotropic functional consequences including the expansion of regulatory T cell population, phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), immune cell differentiation and maturation, apoptosis, expression of proinflammatory cytokines and antigen-presentation	[7]
5	Interleukin (IL)-6 antagonists, granulocyte colony-stimulating factor (GM-CSF) inhibitor, IL-1 antagonists, IL-17 antagonists and antitumor necrosis factor (TNF) agents	By limiting Cytokine storm	[7]
6	Janus kinase (JAK) inhibitors	By inhibiting many proinflammatory cytokines involved in cytokine storm of COVID-19	[7]
7	Anti-TNF agents	By blocking viral entry and detrimental effects of exuberant TNF-α	[7]
8	Anti-IL-17 antagonists	By blocking induction of proinflammatory cytokines	[7]

of molecules involved in inflammation including phospholipases, lipoxygenase, COX-2, thrombaxane, prostaglandins, NO, TNF and IL-12. Curcumin inhibited proinflammants IL-1β, IL-6 and TNF-α by bone marrow derived dendritic cells. Using bone marrow dendritic cells it was found that curcuma blocked STAT 3. Inhibition of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway (JAK/STAT) attenuates cytokine storm. These results suggest that spices have a role in inhibiting and or reducing proinflammatory cytokines levels.

In COVID-19 patients there is a marked decrease in levels of $CD4^+$ cells, $CD8^+$ cells, B-cells and NK cells as well as decrease in monocytes, eosinophils and basophils. Further, there is an increase in proinflammatory cytokines such as IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF and TNF-α (called cytokine storm).[171]Moreover, SARS-CoV-2 increases IKB (inhibitor of nuclear factor κB) degradation leading to the activation of NF-κB signaling and induce IL-6 and TNF-α. Specific blockage of TNF-α and IL-6 antagonists can attenuate inflammation processes; similarly inhibition of JAK/STAT pathway attenuates cytokine storm. Inhibition of NFκB attenuates TNF-α and IL-6 expression. In the present report, most of the spices which we have reviewed have shown to regulate inflammation process, inhibit proinflammatory cytokines and abnormal cytokine release. This is true in case of turmeric and its alkaloids.

In addition, spices have also proven ability as strong antioxidants, free radical scavengers, inhibition of arachidonic acid compounds (responsible for pain, inflammation, swelling, thrombosis) via LOX and COX pathway. All spices reviewed in the present report have shown antioxidant activity by way of DPPH radical scavenging activity, lipoxygenase inhibition, phospholipid peroxidation, hydroxyl radical scavenging activity, superoxide dismutase activity and anti-lipid peroxidation. Owing to the presence of phenolics and flavonoids many of the spices reviewed in the present report have antioxidant activity superior to or equivalent to ascorbic acid. These are responsible in neutralizing invading pathogen. Taken together, spices when consumed daily can have beneficial effects on innate as well as adaptive immunity to human body which gives protection against diseases including COVID-19.

CONCLUSION

Evidence generated from the published literature is compelling to arrive at a conclusion that consumption of spices can improve both innate and adaptive immunity. The developed immunity can potentially fight various diseases including COVID-19. Several clinical trials are in various phases of evaluation to find the role of spices in offering immunity against COVID-19. It is interesting to wait for outcome of clinical trials (Table 3) conducted using spices or products with spice ingredients. The results might be available in the first –second quarter of 2021 to the scientific community. While there is strong evidence on role of spices as immunomodulators and anti-inflammatory agents, we did not find many studies on humans. In our opinion, it is observed that spices are consumed as a part of diet on a daily basis since several years, it may not take huge business sense, apparently researchers and industries are not interested in carrying out human clinical studies on par with pharmaceuticals or biopharmaceuticals. Scientifically also it may be challenging to take Ethics committee approval to find human subjects, in such studies who consume food without spices, for comparison. However, innovative methods of those who consume lesser amount of spices against those who consume higher amounts could be one approach. Addition of selected spices in a superiority trial would be another approach. Also, it would be of great scientific interest if population studies are conducted to document consumption of spices and the populations' immune status. An adequately large sample of population may be assessed for their immune status by analyzing their blood for immunity bio-markers. Such studies could be conducted in partnership with Governmental organizations. In the past decade, there has been greater understanding on human body's immunity with the advent state-of-the-art techniques. With the result, biomarkers have been made available with validated testing methods that were lacking in earlier decades. Hence, it is reasonable to recommend that more human studies on spices and immunity should be conducted to promote healthy living.

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AUTHOR CONTRIBUTIONS

DBAN designed the review, TSJ collected literature, DBAN and TSJ together drafted the work, DBAN reviewed the work.

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DECLARATION OF INTEREST

The authors have no relevant interests to declare.

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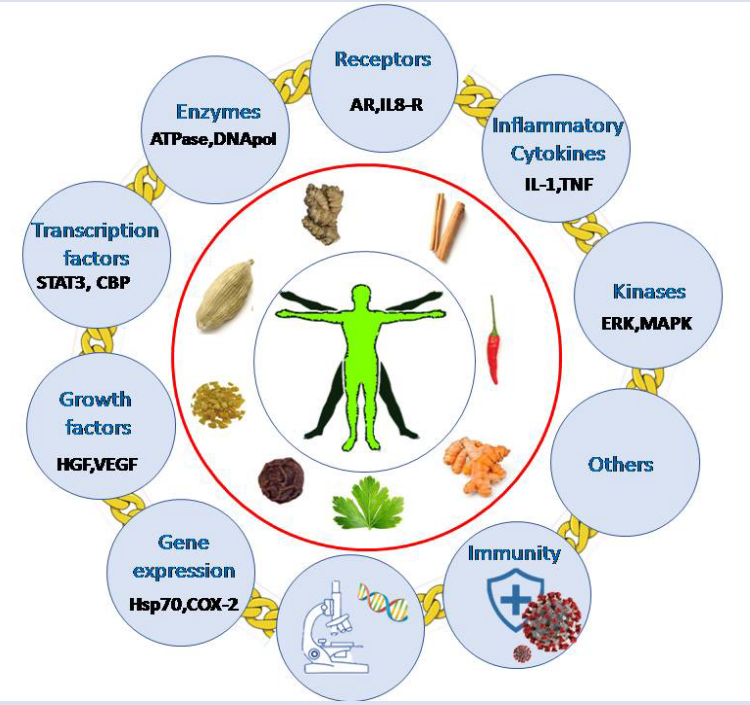
GRAPHICAL ABSTRACT



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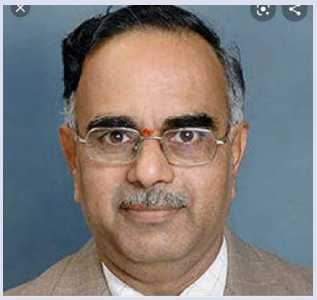
Dr T S Johnson had his doctoral degree from CSIR-CFTRI, Mysore and EMBO World Program Fellowship at The University of Leiden, The Netherlands. He had 23 years of Corporate R&D and 3 years of academic experience. He has published 45 papers of international repute, 5 awarded US and European patents. He has co-edited book on Applications of Plant Metabolic Engineering. He is editorial board member of Plant Biotechnology Reports. He has visited countries like Germany, Israel and Australia. He is recipient of Indian Science Congress Association award, Israel Government's MASHAV and AFST's Young Scientist. His interests include phytoextracts, FSSAI, ASU regulatory.



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