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## POTENTIAL ACTIVITY OF SPICES ON ACE2 EXPRESSION – A MINI REVIEW

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**ABSTRACT:** Spices, nature's gift to mankind are the reservoir of secondary metabolites – alkaloids, flavonoids, saponins, tannins, glycerides, sulfides, and other oxygen/nitrogen compounds that can effectively treat viral infections, bacterial infections, and respiratory problems. Since ancient days they have been used for its anti-inflammatory, carminative, antioxidant, anti-clotting, anti-microbial, anti-pyretic, and cardiotoxic properties. In search of identifying a natural therapy for severe acute respiratory syndrome coronavirus (SARS-CoV) infections, this review investigates the pharmacological nature of some commonly used spices (ajwain, asafoetida, black pepper, cinnamon, clove, coriander, fenugreek, garlic, ginger, long pepper and turmeric) with special reference to the mechanism of vasodilatory property. Among the selected commonly used spices, turmeric and ginger especially have been reported to alter the expression of angiotensin-converting enzyme 2 (ACE2) to exert its vasodilatory property. The study could lead to a novel exploration of vaccines/drugs aided with a detailed investigation of individual bioactive compounds as well as their synergic effects.

**INTRODUCTION:** Techno-savvy life leading us away from the hands of Mother Nature, now urge scholars to search on traditional healthcare techniques, as the world focuses on unveiling medication for the SARS type pandemic for which the WHO has declared a state of public emergency<sup>1</sup>. The naturally gifted bioactive compounds have gained momentum because of their additional benefits of having no side effects and cost-effective, whereas its counterparts show increased resistance by multidrug-resistant microorganisms<sup>2</sup>. The systematic screening of antimicrobial plant extracts may reveal new compounds with the potential to act against SARS coronaviruses.

In ancient days, phytochemicals were the only source of medicines for all types of ailments. Rishis / Scholars insisted upon maintaining a balance between Vata, Pitta, and Kapha<sup>3</sup>, regulating a healthy diet including spices and herbs as well as yoga practices.

Recent researches pictured the potential of spices by investigating the bioactive components rich in secondary metabolites alkaloids, flavonoids, tannins, saponins, glycosides, sulfides, *etc.* Normally phytochemicals have been grouped into two main classes - primary metabolite ensures normal growth and development of the plant. The second being the secondary metabolite that protects plants against pathogens<sup>4</sup> has been analyzed to possess wonderful therapeutic actions capable of treating varied infections/disorders. The extremely fastidious pathogen SARS-CoV has been investigated as a beta-corona virus mediated by ACE2 as one of the major receptors<sup>5</sup>. The extraordinarily large single-stranded ribonucleic

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acid (RNA) genome 26 to 32 kilobases<sup>6</sup>, enables the virus to foot and grab a prominent part physiologically. Corona, otherwise known to be "crown" possesses crown-like spikes<sup>7,8</sup> on the cell surface, locking to the receptor effectively.

The recent SARS-CoV-2 stepped its emergence from Wuhan, China's traditional manufacturing hub. Further, animal species in Wuhan's seafood market have been believed to be the source of SARS-CoV-2. With an incubation period (time required to develop symptom) of 1-14 days<sup>9</sup>, the transmission has been reported through droplet infection from nose/mouth when a person is in close contact with the infected one<sup>10</sup>. Symptomatic infection includes dry cough, fever, fatigue, chest tightening, and difficulty breathing. The infection can also induce apoptosis among intestinal mucosal cells, immune cells, neuronal cells, spleen, thyroid, and kidney tubular cells<sup>11-14</sup>. Other symptoms like gastrointestinal cramps for children can accompany<sup>15</sup>. The infection seems to be fatal for patients reported to have asthma, diabetes, or heart disorders.

The development of a suitable therapeutic agent against the SARS virus has been under investigation since no effective vaccine/treatment has been reported so far. World countries being in the spikes of the corona have been practicing only social distancing/quarantine to control it.

Based on the ACE2 receptor binding property of the severe acute respiratory syndrome coronaviruses (SARS-CoVs), this review investigates the pharmacological nature of some commonly available spices with special reference to its ability to act on ACE2 causing vasodilatory property which may lead to the discovery of new drugs against SARS type outbreaks.

**Receptor for SARS-COVs:** Coronaviruses which are RNA viruses typically enter human cells by binding its glycoproteins on the cell surface. Comparing SARS-CoV, SARS-CoV-2 binds to the ACE2 on human cells with greater affinity resulting in an increased number of infected cases<sup>5</sup>. The virus being mediated by ACE2, researches also indicates possible damage to kidneys as well as Leydig cells and cells in seminiferous ducts in testis<sup>16</sup>.

The enzyme ACE2 normally works on the balanced conversion of angiotensin I (Ang I) to angiotensin II (Ang II) with the aid of angiotensinogen in the liver as well as renin secreted in the kidney. ACE1 converts Ang I to Ang II a vasoconstrictor. ACE2 present in the lungs, heart, arteries, and intestine metabolize Ang II to Ang(1-7), a vasodilator<sup>17-19</sup>. Deficiency of ACE2/deactivation by SARS increases the rate of vasoconstriction obstructing oxygen supply specifically intensifying the problem for patients recorded with cardiovascular diseases and lung disorders<sup>17, 20, 21</sup>. In the older adult case, immunity weakens, which allows the biological system to be susceptible to complications more easily.

Based on its mechanism of action, ACE1 inhibitors/vasodilators along with antibiotics, can regulate the normal functioning of the vascular system. Vasodilators aid the metabolism of angiotensin II enhancing the protective effect on the cardiovascular system. Phytochemicals can better inhibit viruses and can modulate our immunity to evade out the spike of SARS-CoV infections<sup>22</sup>.

### **Pharmacological Nature of Spices - Special Reference to its Ability to Change Ace2 Expression / Vasodilatory Property:**

**Ajwain:** *Trachyspermum ammi*, commonly known as ajwain, traditionally relieves bronchitis, arthritis, sore throat, colds, influenza, asthma, cough, rheumatism, and decongest digestive and respiratory tracts<sup>23-26</sup>. Major biologically active components include thymol, phenolic compounds, para-cymene,  $\gamma$ -terpinene,  $\alpha$ - and  $\beta$ -pinene, carvacrol,  $\alpha$ -terpinene, limonene, dillapiole and dipentene apart from  $\alpha$ -thujene,  $\beta$ -myrcene,  $\beta$ -phellendrene, o-cymene,  $\gamma$ -terpinene, 4-terpineol, dodecane, cis-limonene oxide,  $\beta$ -fenchyl alcohol, tetradecane, ethylene methacrylate, heptadecane and diethyl phthalate<sup>27-29</sup>. Ajwain seeds possess to have stimulant, carminative, anesthetic, diuretic, nematocidal, antiviral, antihypertensive, antiulcer, bronchodilatory, antiplatelet, antitussive, hepatoprotective, antihyperlipidemic, antifungal, antibacterial, antihelminthic, antioxidant, and antiseptic properties<sup>30</sup>. A study on the antihypertensive effect of ajwain proves calcium channel blockage mediating the spasmolytic effects.

The bronchodilatory effects of 0.125 and 0.25 ml/kg of 10 g% boiled ajwain extract proved to be significant compared to that of 6 mg/kg theophylline<sup>31</sup>. Administering thymol (1–10 mg/kg) in anesthetized rats, produced dose-dependent fall in blood pressure (BP) and heart rate, not blocked by atropine at dose 1 mg/kg<sup>32</sup>.

**Asafoetida:** Asafoetida exuded from the rhizome or root of *Ferula asafoetida* has been traditionally used for asthma, bronchitis, flatulence, whooping cough, epilepsy, stomach ache, ulcer, intestinal parasites, and influenza<sup>33</sup>. Some of the bioactive compounds include ferulic acid, coumarins, umbelliferone, luteolin, pinene, sesquiterpenes, terpenoids, etc., along with sulfur compounds. **Table 1** possess properties antispasmodic, anti-diabetic, emmenagogue, expectorant, aphrodisiac, anthelmintic and act as a stimulant to the brain and nerves<sup>34-37</sup>. In anesthetized normotensive rats, it has been analyzed to reduce blood pressure. Alcoholic and aqueous extracts of asafoetida have a potent vasodilation effect by blocking calcium influx into the cell<sup>38</sup>. The extracts have been shown to have decreased the induced contraction by acetylcholine, histamine, and KCl in the isolated guinea-pig ileum. A significant reduction in arterial pressure has been observed in anesthetized rats at doses 0.3-2.2 mg/100g body weight<sup>39</sup>. Substantial antioxidant and vasodilatory properties on Masculine rats at concentrations of 0.05 and 0.2 mg/ml have been reported<sup>40</sup>.

**Black Pepper:** *Piper nigrum* has been demonstrated to have cardio depressant and vasodilator activities through calcium channel blocking<sup>41</sup>. The main active component piperine did not allow BP to decrease beyond a certain limit through associated vasoconstrictor effects. A dose-dependent (1 to 10 mg/kg) decrease in mean arterial pressure (MAP) in normotensive anesthetized rats 41 has been observed in Ca<sup>2+</sup>-free medium (1 to 30 mM). Some of the other active components are  $\alpha$ - and  $\beta$ -pinene, limonene, myrcene, carvone, cryptone, linalool, ar-curcumene, cis-carveol, trans-carveol, 1-terpinen-4-ol, p-cymene-8-ol, myristicin, methyl eugenol, nerolidol,  $\alpha$ -phellandrene, sabinene,  $\beta$ -caryophyllene, piperlongumine, sylvatin, sesamin, diaeudesmin, pipermonaline, piperundecalidine, piperic acid, piperlonguminine, pellitorine, piperolein-B, piperamide, piperettine and (-)-kusunokinin<sup>42-44</sup>.

Traditionally black pepper has been used to treat chronic bronchitis, asthma, constipation, gonorrhoea, paralysis of the tongue, diarrhoea, cholera, chronic malaria, viral hepatitis, respiratory infections, stomach ache, diseases of the spleen, cough, and tumours<sup>45</sup>. Alteration in membrane lipid dynamics and change in the conformation of enzymes in the intestine attribute for its increased absorption, increasing its activity. A study on the inhibition of angiotensin-converting enzyme (ACE) activity by some Indonesian edible plants proved a significant inhibition of 71.3% at 100  $\mu$ g/mL concentration<sup>46</sup>. At higher concentrations piperine exhibited toxic effects – lethal dose 50 (LD<sub>50</sub>) values were shown to be 330 mg/kg in mice and 514 mg/kg in rats<sup>47,48</sup>.

**Cinnamon:** *Cinnamomum zeylanicum* containing essential oils trans-cinnamaldehyde, camphor, eugenol, cineole, procyanidins, caryophyllene oxide, catechins,  $\alpha$ -terpineol, cinnamyl acetate, E-nerolidol, L-borneol,  $\beta$ -caryophyllene, L-bornyl acetate,  $\alpha$ -cubebene, terpinolene, and  $\alpha$ -thujene<sup>49-52</sup> possess anti-inflammatory, antimicrobial, anti-cancer, cardioprotective and cognitive function boosting properties. Owing to its antifungal, antiparasitic, and antibacterial properties, it has been demonstrated to relieve cold and flu<sup>51, 52</sup>. The synergic effect of cinnamon and ginger has been reported to enhance blood circulation. L-NAME-induced hypertensive Wistar rats were examined by administering methanol extract of cinnamon stem bark (MECZ) at various doses 5, 10, and 20 mg/kg. Even for the smallest dose, a drop in mean arterial blood pressure (MABP) by  $46.4 \pm 10.6\%$  has been recognized. At higher concentrations, a sudden drop in MABP from  $176.66 \pm 6.86$  mm Hg to  $83.46 \pm 16.03$  mm Hg has been noted<sup>53</sup>. Cinnamaldehyde has been reported to show a significant inhibition of vasoconstriction induced by endogenous vasoconstrictors, including angiotensin II, following endothelium-independent, Ca<sup>2+</sup> influx, and/or an inhibitory release mechanism<sup>54</sup>.

**Clove:** Since ancient days, *Syzygium aromaticum* (clove) has been investigated to have antidiabetic, anti-inflammatory, antimicrobial, antithrombotic, anaesthetic, pain-relieving, and insect-repellent properties proved to be useful for digestive disorders, cough, dental and ear problems,



muscular cramps, etc. Apart from stimulating blood circulation, it also aids the regulation of body temperature. Clove with honey has been reported to work against asthma. The active principle includes eugenol, thymol, cinnamaldehyde,  $\beta$ -caryophyllene,  $\alpha$ -humulene, eugenyl acetate, carvacrol, and humulene epoxide. Several bioactive compounds, including gallic acid derivatives as hydrolyzable tannins - caffeic, ferulic, ellagic and salicylic acids, flavonoids such as kaempferol, quercetin and its derivatives, essential oils -  $\beta$ -pinene, limonene, farnesol, benzaldehyde, 2-heptanone, and ethyl hexanoate have been isolated from cloves. Eugenol, the main bioactive compound, has been reported to have the potential acting as an antiasthmatic drug as it possesses bronchodilatory and immunomodulatory properties<sup>55-61</sup>. Administering eugenol at doses 40 mg/kg and 80 mg/kg reduced the inflammatory cell infiltration around the bronchioles along with suppression of mucus secretion<sup>61</sup>. Eugenol has been reported to dilate cerebral arteries via multi-modal inhibition of voltage-dependent  $\text{Ca}^{2+}$  channels<sup>62</sup>. Vasoconstrictor response elicited by noradrenaline (10 nmol) injection has been dose-dependently and completely inhibited by eugenol at dose range 0.1-1 mM<sup>63</sup>.

**Coriander:** Biopotency of *Coriandrum sativum* is mainly reported by the presence of coriandrol and vebriniol and other minor compounds  $\alpha$ -pinene,  $\beta$ -pinene, limonene, camphor,  $\gamma$ -terpinene, borneol, cineole, geraniolcitronellol,  $\beta$ -caryophyllene, geranyl acetate,  $\beta$ -phellandrene, linalyl acetate, thymol, elemol, caryophyllene oxide and methyl heptenol<sup>64, 65</sup>. A drop in arterial blood pressure of anesthetized animals has been noted at dose 1-30 mg/ml crude extract, partially blocked by atropine. Vasodilatation against phenylephrine and  $\text{K}^+$  (80 mM)-induced contractions in rabbit aorta was also reported. The study reveals the anti-hypertensive effect of coriander ascribed to its diuretic,  $\text{Ca}^{2+}$  channel blocker, and cholinergic property<sup>66</sup>.

**Fenugreek:** *Trigonella foenum-graecum*, commonly known as fenugreek, possesses antipyretic, hypoglycaemic, antihypertensive, hepatoprotective, hypocholesterolemic, antiulcer, antibacterial, anthelmintic, antifatigue, and appetite stimulant properties. Being a good source of saponins such as yamogenin, tigogenin, and diosgenin, fenugreek

exhibits anticancer, cardio-protective, contraceptive, and antiaging activities. Some of the bioactive components identified include trigonelline, choline, gentianin, carpaine, betain, tannic acid, gitogenin, rhaponticin, quercetin, rutin, vitexin, isovitexin, etc.<sup>67-72</sup> In unilateral nephrectomised DOCA-salt hypertensive rats, administration of methanolic fenugreek extract (30 mg/kg/day) for four weeks showed a significant reduction in blood pressure and a higher concentration 100mg/kg/day for six weeks required for fructose hypertensive rats<sup>67, 73</sup>.

**Garlic:** *Allium sativum* is rich in organosulfur compounds alliin, allicin, diallylsulfide, diallyl-disulfide, diallyltrisulfide, ajoene, allyl methyl thiosulfonate, 1-propenyl allylthiosulfonate,  $\gamma$ -L-glutamyl-S-alkyl-L-cysteine, and S-allyl cysteine has been reported to possess antioxidant, cardio-protective, hypolipidemic, anticancer, antiinflammatory, foreign compound detoxification, radioprotection, immuno-modulatory, antidiabetic, antiobesity and antibacterial properties<sup>74-83</sup>. Garlic enhance epithelial dependent vasodilation by increasing the production of NO and hydrogen sulfide, inhibiting the angiotensin-converting enzyme<sup>84, 85</sup>. In the presence of thiols, the sulfur compound allicin easily degraded into organic diallyl polysulfide providing  $\text{H}_2\text{S}$ . A study conducted in Wister rats reveals a significant balance between T-helper 1/T-helper 2 by combining garlic with levamisole<sup>79, 86</sup>. Selenized garlic polysaccharides promote lymphocyte proliferation, enhances interferon- $\gamma$  and IL-2, and increase the serum antibody titer in 14 dayold chickens<sup>87</sup>.

Reports reveal some adverse effects while consuming raw garlic or garlic powder which include bronchial asthma. Allicin and other thiosulfinates have been reported as highly unstable compounds that when garlic is damaged, the formation of hundreds of organo-sulfur compounds results for which consumption of fresh raw garlic adds digestive disorders and allergic problems<sup>88</sup>. Pulmonary vascular responses to allicin (0.1–1.0 mg) studied in anesthetized cats and isolated lung of rat showed a significant vasodilatory activity<sup>89</sup>.

**Ginger:** Ginger (*Zingiber officinale*) an expectorant in relieving asthma, cough, tuber-

culosis, digestive disorders, colds, influenza has been found to possess anti-inflammatory, antimicrobial, antimutagenic, chemopreventive hepatoprotective, and antiemetic properties. Biological potency is due to the presence of sesquiterpene, predominantly zingiberene,  $\beta$ -bisabolene, gingerols, gingerenone, zingerone, and shogaols. Apart from these compounds, cineol, phellandrene, citral, borneol, citronellol, geranial, linalool, farnesene, limonene, zingiberol, camphene, and zingibain have also been reported<sup>90,91</sup>.

A study on inhibition of lipid peroxidation by white ginger reveals antihypertensive effect by inhibiting the angiotensin-I-converting enzyme (half-maximal effective concentration ( $EC_{50}$ ) = 87.0  $\mu$ g/mL). The study extends the greater advantage of red ginger exhibiting a better inhibitory effect ( $EC_{50}$  = 27.5  $\mu$ g/mL)<sup>92</sup>.

The effect of SND (Sini decoction) – a Chinese medicinal formulation combining Aconite, Licorice, and Ginger rhizome on the renin-angiotensin system shows an increased expression of ACE2 in lung tissue. Sepsis-induced acute lung injury in mice has been ameliorated by SND via regulating the ACE2-Ang (1-7)-Mas axis and inhibiting the Mitogen-activated protein kinases (MAPK) signaling pathway<sup>93</sup>.

**Long Pepper:** *Piper longum* possesses immunomodulatory activities, stimulating properties, anti-inflammatory properties, hepatoprotective activity, antibacterial properties, hypocholesterolaemic activities, and antiasthmatic benefits applicable for treating chronic bronchitis, cough, cold, etc. The active bioactive compounds include piperine, piperlongumine, guineensine, chabamide, and pellitorine.

Compounds methyl piperine, iperonaline, piperettine, asarinine, piperundecalidine, piperlonguminine, pregumidiene, brachystamide, brachystamide-A, brachystine, pipericide, longamide, tetrahydropiperine, dehydro-piperonaline, piperidine, tetrahydropiperlongumine and trimethoxycinnamoyl-piperidinone has been found in the root of long pepper. The essential oil of the fruit contains caryophyllene, pentadecane, bisabolene, thujone, terpinolene, zingiberine, p-cymene, p-methoxyacetophenone and dihydro-carveol apart

from piperine<sup>94-98</sup>. Maximum ACE inhibitory activity has been recorded by ethyl acetate and butanol fractions of black pepper with half-maximal inhibitory concentration ( $IC_{50}$ ) value of  $1.40 \pm 0.07$  mg/ml and  $1.75 \pm 0.43$  mg/ml, respectively<sup>99</sup>.

**Turmeric:** Traditionally, *Curcuma longa* has been used as an herbal medicine for chronic anterior uveitis, urinary tract infections, conjunctivitis, rheumatoid arthritis, skin cancer, chickenpox, smallpox, wound healing, and liver ailments<sup>100</sup>. It has been analyzed to have an anti-asthmatic property (20 mg/kg body weight) antagonizing the tracheal contraction induced by histamine and acetylcholine in guinea pigs<sup>101</sup>.

A study performed on male Sprague Dawley rats expresses inhibition of the myocardial fibrotic process by altering expression of Ang II AT1/AT2 and ACE2 receptors by curcumin (150 mg/kg/day)<sup>102</sup>.

Further, AT1 receptor antagonism, activation of the AT2 receptor, and ACE2 up-regulation have been noted which helps to reduce blood pressure. Curcumin, a bioactive component in *Curcuma longa* has been studied to induce sustained vasodilation in lower doses, peaking by 20 seconds whereas, higher dose curcumin initiated dilation, peaking by 20 seconds, followed by a secondary constriction, peaking by 60 seconds<sup>103</sup>.

The major bioactive principle includes curcuminoids (curcumin, demethoxycurcumin, and bis-demethoxycurcumin), non-curcuminoids such as sesquiterpenoids - bisabolanes, elemene, turmerones, furanodienone, curcumol, bisacurone, curdione, phellandrene, sabinene, cineol, borneol, zingiberene, sodium curcuminates, ar-turmerone and curlone records anti-inflammatory, anticancer, antimicrobial, antioxidant, antitumor, antitussive, hepatoprotective, antispermatic, hypolipidemic, antiulcer, antifertility, antivenomic, antiemetic, insect repellent and antidepressant activity having the potentiality to alleviate rheumatoid arthritis, neurodegenerative diseases, cardiovascular diseases can also prevent selenium and ionizing radiation-induced cataractogenesis<sup>104-108</sup>.

**TABLE 1: VASODILATORY MECHANISM OF SOME COMMONLY USED SPICES**

| Botanical name  | Vasodilation mechanism  | Major bioactive compounds   |
|---|---|---|
| Ajwain ( <i>Trachyspermum ammi</i> ) <sup>32</sup>                | Dose-dependent fall in blood pressure observed in anesthetized rats by administering thymol (1–10 mg/kg) – may be by calcium channel blocking.  | Thymol.   |
| Asafoetida ( <i>Ferula Asafoetida</i> ) <sup>34, 35, 37, 39</sup> | At doses, 0.3–2.2 mg/100 g body weight - act as calcium channel blocker in anesthetized rats.   | Sulfur compounds: di-(2-methyl-1,3-oxathiolanyl)methane, trans-propenyl-sec-butyl disulfide, thiophene, cis-propyl sec-butyl disulfide, 2-methyl-2-methylthiopropionic acid and methyl-1-(methylthio)propyl disulphide. |
| Black pepper ( <i>Piper nigrum</i> ) <sup>41, 48</sup>            | A dose-dependent (1 to 10 mg/kg) decrease in mean arterial pressure (MAP) in normotensive anesthetized rats in Ca <sup>2+</sup> -free medium (1 to 30 mM). Induced hypertension, by chronic NO synthesis inhibition, reduced via calcium channel blockade in rats with piperine dose 20 mg/kg/day.  | Piperine.   |
| Cinnamon ( <i>Cinnamomum zeylanicum</i> ) <sup>53, 54</sup>       | A drop in mean arterial blood pressure (MABP) by 46.4 ± 10.6% for 5 mg/kg of MECZ stem bark. MABP decreased by 12.5%, 26.6% and 30.6% at the doses of 5, 10 and 20 mg/kg. Inhibition on vasoconstriction induced by endogenous vasoconstrictors including angiotensin II, following endothelium-independent, Ca <sup>2+</sup> influx, and/or an inhibitory release mechanism. | Cinnamaldehyde, camphor.  |
| Clove ( <i>Syzygium aromaticum</i> ) <sup>61, 63</sup>            | Eugenol at doses 0.1-1 mM, showed inhibition of, vasoconstriction induced by noradrenaline (10 nmol) – by calcium channel blocking.   | Eugenol.  |
| Coriander ( <i>Coriandrum sativum</i> ) <sup>64, 66</sup>         | Reduction in arterial blood pressure of anesthetized animals have been noted at dose 1-30 mg/ml crude extract - Ca <sup>2+</sup> channel blocking and cholinergic property.   | Coriandrol, pinene, terpinene, geranyl acetate, camphor, and geraniol.  |
| Fenugreek ( <i>Trigonella foenum-graecum</i> ) <sup>67, 73</sup>  | In DOCA-salt hypertensive rats - methanolic fenugreek extract (30 mg/kg/day) for four weeks showed a significant reduction of blood pressure. Fructose hypertensive rats – 100 mg/kg/day for six weeks required – the serotonergic antagonistic property may involve.   | Saponins especially diosgenin.  |
| Garlic ( <i>Allium sativum</i> ) <sup>77, 84, 85, 89</sup>        | Improvement in cardiac performance of 23% and 17%, observed in isolated hearts of Control + Aged Garlic Extract (AGE) and Metabolic Syndrome + AGE rats. Production of NO and hydrogen sulfide, inhibiting the angiotensin-converting enzyme.   | Organo-sulfur compounds mainly allicin, diallylsulfide, diallyldisulfide, diallyltrisulfide, E/Z-ajoene, S-allyl-cysteine, and S-allyl-cysteine sulfoxide (alliin).   |
| Ginger ( <i>Zingiber officinale</i> ) <sup>90-93</sup>            | White ginger reveals antihypertensive effect by inhibiting angiotensin-I converting enzyme (EC <sub>50</sub> =87.0 µg/mL), red ginger exhibiting a better inhibitory effect (EC <sub>50</sub> =27.5 µg/mL) - increased expression of ACE2 in lung tissue.   | Zingiberene, β-bisabolene, gingerols, gingerenone, zingerone and shogaols.  |
| Long pepper ( <i>Piper longum</i> ) <sup>96, 99</sup>             | ACE inhibitory activity by Ethyl acetate and butanol fractions of <i>Piper longum</i> with an IC <sub>50</sub> value of 1.40 ± 0.07 mg/ml and 1.75 ± 0.43 mg/ml. The pronounced hypotensive effect at dose 1mg/kg body weight of ethanolic extract – calcium channel blocking - nitric oxide and prostacyclin pathways involved.  | Piperine<br>Dehydropiperonaline.  |
| Turmeric ( <i>Curcuma longa</i> ) <sup>102</sup>                  | Inhibition of the myocardial fibrotic process by altering expression of Ang II AT1/AT2 receptors and ACE2 by curcumin (150 mg/kg/day) observed in male Sprague Dawley rats - activation of the AT2 receptor and ACE2 up-regulation.   | Curcumin.   |

Comparing the mechanism **Table 1** through which the spices act as vasodilators, interestingly, ginger and turmeric have been reported to follow a different pathway. While most of the selected spices have been reported as calcium channel blockers, ginger and turmeric change the expression of ACE2 to exert its vasodilatory

property. This observation can give new hope in the field of vaccine/drug development against SARS-CoV infections. With the capability of up-regulating ACE2, turmeric as well as ginger could probably be capable of freeing the ACE2 receptors from the spikes of SARS coronaviruses.

**CONCLUSION:** Since its origin which dates back thousands of years, spices have been a rich source of immunity. Apart from its aroma, colour, and flavour, the consumption of spices has been implicated in preventing immunological disorders, cardiovascular problems, and metabolic disorders, being rich in secondary metabolites, alkaloids, flavonoids, saponins, terpenoids, steroids, anthocyanin, tannin, *etc.* Turmeric and ginger acting on ACE2 can be investigated in detail along with its synergic effect. Competitive binding, the extent of affinity towards the ACE2 receptor can also be assessed, which could emerge out vaccine/drug for SARS-CoV infections. Every man-made system mimics nature, and Mother Nature will have its solution. Naturally immunized biological systems can resist any epidemics/pandemics, change in food habits can bring about an enormous change. Traditional food habits, along with regular yoga and meditation, enable the biological system to face any challenge, which includes SARS.

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