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Spices, Unpacked Diet, Bio Actives and Immunity: Indian Health & Pandemic

Dr. Utkarsh Ghate [1*], Dr. Hema Kulkarni [2]
[1]Ecologist, BAIF, Warje town, Pune city, PIN 411 058.Maharashtra state, India*
[2]Assistant Professor, Zoology, Model College, Durg city, Chhattisgarh state, India

ABSTRACT

Spices and vegetable rich, home cooked diet prevails in Asia, especially in India which is rich in polyphenols. This could have led to higher immunity and health, which is evident from the 3-4 time lower prevalence (< 10% population) and mortality (0.1% population) than the western countries. Mainly processed foods (packed and in hotels, with preservatives or additives therein, besides refined flours and vegetable oil/ trans fats) prevalent in developed countries can damage immunity. Consequent advanced glycation end products (AGEs) prevalence is a health risk. Polyphenols, saponins, salicylates and greater traditional, herbal medicines in the Asian diet, besides lesser vaccination/ flu shots/ antibiotics use may protect immunity, unlike in EU/ USA. Quercetin, piperine and isothiocynate (an organosulfur compound) in red onion, black pepper and mustard seed oil respectively may be the key health ingredients and anti-microbial/ anti-viral agents. Herbal tea from *Terminalia arjuna* L. tree bark is identified as potential COVID-19 cure alone or as adjuvant, as triterpenes in it build immunity. The Indo-Mediterranean diet with less refined flours, red meat and liquor, tobacco than the western countries may be healthy like the Oriental (Japanese) diet. Consumption extent of spices, especially mustard, is reported by others to be negatively correlated with corona incidence across 163 countries, as we too show here. We explain the preventive effect of 3 superfoods on COVID-19: red onion, black pepper & mustard.

Europe and USA population miss the benefit of antioxidant quercetin content of the pungent red onion, as mild varieties are preferred, viz., white/yellow onion/shallot. Black pepper is healthier that chilly but the latter is commonly cooked by ignorance. Mustard oil that is common in India has high COVID-19 deterrence due to glucosinolates i.e. sulfur compounds. However, canola and rapeseed prevalent in EU & USA are bred for lower glucosinolate content to avoid pungency, but with no health benefits.

Keywords: COVID-19, Ayurveda, Indo-Mediterranean diet, superfoods, antibiotics

INTRODUCTION

Phytopharmaceuticals are in discussion and demand again now due to limitations of the modern medication in containing the recent COVID-19 epidemic. Immunity is the hottest topic and research to protect or enhancing it, including phytochemicals is making headlines. Medicinal plants sector is growing rapidly worldwide recently, due to higher benefits in case of chronic ailments and lesser adverse drug reactions (ADR) or a safety perception in the society (Ventola. 2010). This has triggered the World Health Organization to develop traditional medicine strategy for 2014-23 (WHO, 2019). There are projections that medicinal plants/ botanicals market will grow to $ 5 trillion by 2050 (Kala *et al.*, 2016). India is no exception and is in fact leading the tide with herbs such as Holy Basil (*Occimum sanctum* L.) and Mint (*Mentha piperita* L.) are common in herbal tea.

AYUSH, i.e. Indian traditional medicinal systems (Ayurveda, Yunani, Siddha, Homeopathy etc.), industry is worth Rs. 1600 billion i.e. $ 20 billion in 2022 (Anon, 2020a). It grew 7 times its value in 2014, supporting about 40,000 microenterprises and created huge

* Corresponding Author

rural employment. The global herbal market is about $ 120 billion i.e. 6 times, with huge export scope (Ghate & Wele, 2022).

Recent global pandemic (COVID-19) indicates high risk of future epidemics, starting a decade ago with SARS and Zica virus, for instance, though these remained local. This underlines the need to build strong immunity as counter strategy to avoid future global microbial infections (Salazar *et al.*, 2022). Hence, there is recent global spurt in immunity building drugs from botanicals. Here we elucidate the contribution of spices and herbs in building immunity with the Indian insights and global comparisons. We discuss the COVID-19 damages across countries by economic category and its relation to diet difference and herbal medications for immunity boosting/ relief/ cure.

MATERIALS AND METHODS

The following parameters are used to measure the COVID-19 intensity:

(1) prevalence – no. of patients/ 1 million population,

(2) mortality – no. of deaths/ 1 million population,

(3) fatality – as % of patients.

These data represent the last 3 years cumulative numbers (01st April 2020- 31st March 2023) of the top 99 countries except China where data certainty was low (Anon, 2022a). World Bank open database is used to deduce the income level data of countries is obtained from the year 2019 (Anon, 2022b). COVID-19 was declared as non-epidemic in mid-2023.

Data on the spice consumption and their bioactive ingredients and their action on COVID-19 were gathered from literature as referred later. Same way their other health benefits are also mentioned.

RESULTS

The country-wise data on COVID-19 intensity are provided below. Table 1 and Figure 1 depict its country average in 3 economic categories: high, middle and low. COVID-19 prevalence in the high income countries (28% of population affected) is 2 times that in the low income countries (14% of population affected). The mortality however is only 11% higher in the rich countries than the poor countries. This can relate to the better medical facilities in the former, to save life such as ventilators or oxygen pumps. The question here is why more population in richer country is affected despite (a) low population density and (b) digital lifestyle to maintain physical distance with just 2-4 inmates per house often, about 50% or lesser than the middle or low income countries levels.

Table 1. Mean COVID-19 intensity in countries by income classes

	Income	Prevalence/ 1 M population	Deaths/ 1M population	Tests/ 1M Population	Positivity %	% Deaths/ cases	N
HIC	High	2,87,233	2,073	32,23,011	8.9	0.72	51
MIC	Medium	1,78,314	1,478	18,39,195	9.7	0.83	39
LIC	Low	1,42,973	1,785	12,19,632	11.7	1.25	9

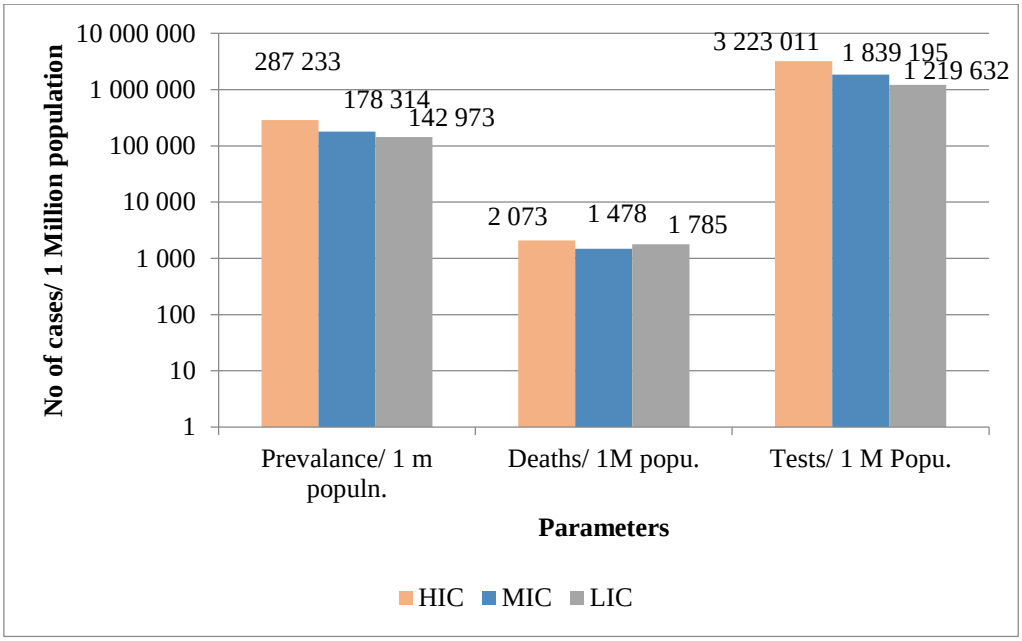

Figure 1. COVID-19 intensity and country income classes

Table 2 depicts the countries most affected by the most affected by the COVID-19. India stands 2nd the world after USA (cases – 0.24 million/ million population i.e. 24% of people, deaths – 2,976/ million people). But India has only 12% of the prevalence (3% prevalence) and deaths (368/ million) compared to the USA (24% prevalence, 2,976 deaths/ million). This is despite the fact that India has much higher population density than USA, so has higher infection chance as it's a contagious disease. Same is the case with Europe – 28% population infected and mortality of 2,151/ million population. Thus, Indian immunity may be higher as it's the shield against COVID-19 as there is no specific drug as yet developed for COVID-19, despite the vaccines. The pattern today is similar to the scenario in early 2021 (Ghate & Kulkarni, 2021) prior to the vaccination drive, which indicates natural immunity. India's south & east Asian neighbors seem to have lower COVID-19 intensity and hence, perhaps higher immunity. China data are unavailable/ questioned so are not used. The infection and mortality rates are also low in Africa having little food processing industry and ample sunlight. So no African country is listed in the top 25 countries listed in Table 2 and most of them are rich.

Table 2. COVID- 19 intensity in top 25 countries and India (31st March 2023)

	Country	Tot Cases/ 1M population	Deaths/ 1M population	Tests/ 1M Population
	WORLD avg.	87,571	875	
1	USA	3,16,542	3,440	34,98,311
2	India#	31,775	377	6,54,124
3	France	6,05,398	2,522	41,39,547
4	Germany	4,56,550	2,023	14,58,359
5	Brazil	1,72,486	3,249	2,96,146
6	Japan	2,65,773	586	7,70,930
7	S. Korea	5,98,150	666	3,07,892
8	Italy	4,25,656	3,132	44,65,893
9	UK	3,56,557	3,043	76,28,357
10	Russia	1,54,428	2,722	18,75,095

11	Turkey	1,99,186	1,186	19,02,052
12	Spain	2,95,022	2,566	100,82,298
13	Vietnam#	1,16,490	436	8,67,342
14	Australia	4,32,610	755	30,24,116
15	Taiwan	4,28,526	787	12,86,903
16	Argentina	2,18,320	2,836	7,76,264
17	Netherlands	5,00,016	1,336	15,09,718
18	Iran	88,126	1,687	6,43,478
19	Mexico#	57,094	2,534	1,49,809
20	Indonesia#	24,152	577	4,08,975
21	Poland	1,71,527	3,157	10,18,463
22	Colombia#	1,23,490	2,769	7,17,327
23	Austria	6,62,148	2,431	233,02,116
24	Greece	5,72,871	3,526	99,09,078
25	Portugal	5,49,464	2,594	45,37,462

Note: 20 (80%) of the 25 countries listed are high income category ($> 15/day/ head), rest medium income. No low income country is observed here as they have low mortality. #- Medium income
Source: https://www.worldometers.info/coronavirus/

DISCUSSION

Confounding Factors

Before discussing the diet and spices, the study focus here, a few disclaimers or confounding factors need mention that may affect the results and not be fully adjusted due to data unavailability or computational issues. These include Vitamin D deficiency as causing higher COVID-19 risk (Griffin *et al.*, 2020). US & EU population spends much time in air conditioned and sunlight deficiency in the houses, offices or cars. Indians, however mainly work in the farms (especially rural) or roadside petty shops, exposed to sunlight. About 40% of Europeans are vitamin D deficient but only half of it (20%) in India as found before COVID-19 (Amrein *et al.*, 2020).

Higher age of the population in EU & USA could make them more vulnerable to the pandemic due to lower innate immunity (Ghate & Kulkarni, 2021). Lower COVID-19 intensity in India/ Asia than in the west could also be due to the higher microbial "Exposure" may also explain the, due to the poor hygiene in the former countries so the body gets accustomed to face microbes (Kumar & Chander, 2020). Indeed, the slums in India did not show explosive Corona intensity or mortality while it was high among the elite section. Immunity may also be genetically driven (Chinnaswamy, 2020). Asians have got a protein D614 mutation, unlike Europeans, which may make Asians stronger than the Europeans (Zhang *et al.*, 2020). Higher COVID-19 resistance in India/ developing countries may also be due to BCG vaccine for TB discontinued in EU/ USA (Escobar *et al.*, 2020).

Finally, the importance of fast, processed, packed food in lowering the immunity in the west and metros in the developing world is already underlined (Ghate & Kulkarni, 2022). Many Europeans regularly receive flu shots in the winter, a practice unheard in India. Excess antibiotics use and medication in the west may also reduce the body's ability to resist and recoup in the infections. Bottled drinking water and antibiotics overuse in the developed countries and metros globally can also impact immunity.

Spices

Spices are produced and consumed much more in Asia than the western countries and India leads here with double consumption (2 kg/ head/ year) than the global/ western average

(Ghate & Kulkarni, 2021). Chilli comprises nearly 20% of the 5 gram/day/head spices consumed, and Turmeric, Ginger, Mustard, Coriander, Cumin are nearly equal, the 5 adding to 80% of the spices consumed on average in India. Chilli has not anti-viral properties unlike rest of the spices as the stud quoted.

Table 3 depicts the mechanisms of prevention or relief from COVID-19 by various commonly consumed spices in India. Most consumed spices and their main bioactive ingredient include Turmeric (Curcumin) (Roberts *et al.,* 2020), coriander (Quercetin, Apigenin, Vitamin C) (Singh *et al.,* 2021), Mustard (Allyl isothiocyanate) (Guijarro-Real *et al.,* 2021), besides Onion (Quercetin, Taxifolin) are studied for action on COVID-19 virus (Negi *et al.,* 2021).

Table 3. Main spices consumed in India & mechanism of action on COVID-19

SPICE	BIOACTIVE	MECHANISM
Turmeric	Curcumin	1) inhibits angiotensin-converting enzyme 2 (ACE2), 2) binds to spike glycoprotein- RBD, and PD-ACE2,
Pepper	Piperdardiine, Piperanine	Good affinity to the receptor due to more lipophilic character and also due to hydrogen bonding
Mustard	Allyl isothiocyanate	A derivative of Sinigrin – allyl isothiocyanate – potently inhibited 3CLPro activity
Ginger	8-Gingerol, 10-Gingerol	block the spike (S) protein from binding to the ACE2 receptor or act as an inhibitor for MPro
Holy Basil	Ursolic acid**	inhibition of main protease of SARS-CoV-2

Note: **- and vicenin, sorientin 4'-O-glucoside 2”-O-phydroxy-benzoagte

Cancer incidence globally is 197 per 100,000 population but is higher in EU (363) USA (387) and very low in India (89 per 0.1 million) (Bray *et al.,* 2018). This may be related to higher Turmeric consumption in India than USA, as it contains the polyphenol “Curcumin” known to be anti-cancerous (Aggarwal *et al.,* 2011). Lipid medium such as milk with turmeric is prevalent in India and may enhance Curcumin bioavailability as polyphenols are lipid soluble, but aquaphobic. Asthma incidence in Europe is high – 20 to 25% population affected, which is 2 times that in India (Anon, 2018), indicating lower immunity in Europe *prima facie*.

Spices also contain “Salicylic Acid” that is precursor of aspirin and has similar medicinal effect (Paterson *et al.,* 2006). This may explain the efficacy of drinking spice decoction resulting in much lower intensity of COVID-19 in India than the western countries (Ghate & Kulkarni, 2021). For, Govt. of India advised people to sip spice decoction (“Kadha” in vernacular) daily vide Ayurveda- the ancient Indian medical system (Anon, 2020b). Its working mechanism is also explained by scientists theoretically and through actual field data (Sharma, 2020). Holy basil (*Occimum sanctum* L., "Tulsi" in vernacular), commonly mixed in the herbal tea, has many bioactive ingredients including Eugenol, among the strongest antioxidant molecules (Upadhyay, 2017). Kunnumakkara *et al.* (2021) too elaborated on mechanism of various spices’ molecular action on COVID-19 and show its intensity map across the world in December 2020-january 2021 period with nearly blank in southern Asia & Africa!

Chilli for instance has strong antibacterial effect rather than viral properties (Marini *et al.,* 2015). But it has replaced globally the Black paper i.e. “Black gold” that is healthy and antiviral (Mair *et al.,* 2016) and the leading spice once that changed the world history by triggering voyages of Columbus and Vasco de Gama. In fact, Chilli consumption can reduce the healing effect of salicylate in other spices (Cruz *et al.,* 1999). But, the people are ignorant of differential health effects of the 2 peppers and crazy after pungency. Black pepper

consumption seems healthier than the red Chilli peppers, as the former improves bioavailability of other spices bioactive ingredients (Aggarwal *et al.,* 2011). Ginger (Chang *et al.,* 2013), Mustard (Goetz *et al.,* 2020) & Turmeric are also anti-viral (Kunnumakkara *et al.,* 2017; Shahidi & Hossain, 2018). Consumption extent of spices is negatively correlated with corona incidence across 163 countries as spices help in immunity (Elsayed & Khan, 2020). We now briefly review 3 important phytochemicals in the key spies that may help build human immunity and act as "slow medicine" akin to the 'slow science" concept indicated for the traditional ecological knowledge (Gadgil *et al.,* 2000).

Mustard – Allyl Isothiocyanate

European researchers have shown that the Mustard oil is antiviral & SARS inhibitor (Goetz *et al.,* 2020). It is a major cooking oil in Northern India so it may have protected the population here against COVID-19 despite the poverty and high population density. Chinese researchers have shown the negative correlation between COVID-19 prevalence and Mustard imports across nations (Zhan *et al.,* 2022). Mustard has highest glucosinolates i.e. sulfur compounds that are highest in the Brassicaceae family, comprising of broccoli, radish etc. (~25.9 mg g−1 dw) and rich in sinigrin. But their pungent and bitter taste leads to lower consumption (Bell & Wagstaff, 2017). Canola and Rapeseed prevalent in EU & USA has much reduced levels through plant breeding aimed at lower pungency & bitterness (Daurova *et al.,* 2022). So crop improvement strategy for comforting taste has reduced the health benefit here.

Onion – Quercetin

Quercetin (Que) and its derivatives are naturally promising bioactives. It has antidiabetic, anti-inflammatory, antioxidant, antimicrobial, anti-Alzheimer's, antiarthritic, cardiovascular, and wound-healing effects, as well as its activity against different cancer cell lines (Salehi *et al.,* 2020). Quercetin is an emerging super-molecule, is water insoluble and its bioavailability is low, and in pure form it is easily excreted. When conjugated with amino acids, it improves the physicochemical properties and overcomes cancer multidrug resistance (MDR) i.e. the resistance to the use of anticancer drugs. Conjugates can show less hydrolysis and higher water solubility (Arifian *et al.,* 2022).

Red onion shell displayed highest levels of Quercetin (1,243 mg/kg) in India from laterite soil in Chhattisgarh state presumably due to the metabolic stress (Ghate *et al.,* 2019). This variety called "Nasik red" is popular country wide but not abroad who think it's pungent. Red onion was also found be most Quercetin rich variety in Russia (Chernukha *et al.,* 2022). Ethanolic extract from red onion husks exhibited the highest antioxidant values {mean of 2017.34 _mol-equiv. Trolox/g raw (TACORAC) and 2050.23 _mol-equiv. DQ/g (TACFRAP)}. Much lower levels of antioxidants were seen in the White onion. Red onion husks had the highest content of flavonoids, at an average of 1915g-eq. DQ/g and 321.42 g-eq. DQ/g for ethanol and water, respectively. But yellow onion husks exhibited 544.06 g-eq. DQ/g and 89.41 for ethanol and water, respectively i.e. 75% milder. Quercetin and its glycosides were the most abundant flavonoids.

Study in Norway (Slimestad *et al.,* 2007) also has shown Red onion to possess nearly 415-1917 mg/kg flavonols (Fresh Weight- FW), i.e. about 2 times that in the Yellow onions (270-1187 mg). However, quercetin content in the bulb portion in USA showed yellow varieties to be more quercetin rich (70-238 mg/kg) than the Red varieties (119-282 mg/kg) though the white Onion had only trace of quercetin (Patil *et al.,* 1995). Further, this result was in contrast with an earlier study red onion to be richer in quercetin (Kiviranta *et al.,* 1988). Onion shell is richer in quercetin than the edible part sampled (Pawar *et al.,* 2021). Europe

and USA population may be missing the benefit of antioxidant properties higher quantities of quercetin or its glycosides, due to the less pungent white/ yellow Onion/ Shallot.

Black Pepper – Piperine

Black pepper (*Piper nigrum* L.) called as "black gold" long ago changed the World History as it led Columbus to discover America and Vasco de Gama landed in India. Its cousin *P. longum* L. is called long pepper and has similar properties but considered more medicinal. Black pepper's relative value and trade has much reduced today due to the rapid increase of Chilli (*Capsicum annum* L.) globally that has fewer health benefits. Black pepper's main bioactive ingredient is Piperine that is amide alkaloid with multifarious activities such as antioxidant, anti-inflammatory, antihypertensive, anticancer, hepatoprotective, pro-fertility, neuroprotective, and bioavailability enhancing. Piperine alters gastrointestinal disorders, drug-metabolizing enzymes, and several drugs bioavailability such as Curcumin (Kesarwani & Gupta, 2013; Tripathi *et al.*, 2022).

Furthermore, binding chemistry of piperine and curcumin via π–π intermolecular interactions enhances curcumin's bioavailability, which facilitates curcumin to bind RBD Spro and ACE-2 receptors of host cell, thereby inhibiting the entry of virus inside the host. The above study by Tripathi et al (2022) at the Indian Institute of Technology (IIT) Banaras Hindu University, explains pharmacology of the benefit of Piperine in preventing and treating many chronic ailments, including drug delivery and nanotech. Piperine alkaloid can thus be a "super-molecule" in future like quinine. Antibody formation on spice decoction consumption in treating COVID-19 is reported (Eapen, 2021).

Ayurveda Herbs Effect on COVID-19

Several Indian spices are known to improve immunity & health, including in COVID-19 (Kunnumakkara *et al.*, 2021) and cancer (Aggarwal *et al.*, 2011). Use/ export of herbs/ spices/ botanicals and traditional medicinal systems such as Chinese and Indian (Ayurveda/ Siddha) is growing rapidly globally as complementary and alternative medicine (CAM) including as "adjuvants" to modern medicines so as to reduce Adverse Drug Reaction (ADR) of chemotherapy or radiation and NSIADs (Ghate & Wele, 2022). Ashwagndha i.e. Indian Ginseng (*Withania somnifera* (L.) Dunal), a traditional tonic, is among the most potent of Indian herbs considered a Rasayana (rejuvenating, anti-aging medicine) causing longer, healthier life and is consumed in many Indian families routinely and is also a COVID-19 deterrent (Borse *et al.*, 2021) vide the study by Pune university. "Chyavanprash" a commonly consumed Ayurvedic tonic in many families routinely has many such Rasayana herbs is an immunity builder and contains mainly Triphala (3 myrobylan fruits- Amla- *Phyllanthus emblica* L., Behera- *Terminalia bellirica* (Gaertn.) Roxb., Harra- *T .chebula* Retz.) (Ghate & Kulkarni, 2020). These are in the top ranks of the global 3,100 food items antioxidant value (Carlsen *et al.*, 2010). This may explain the strong immunity in India.

Pune university studied on COVID-19 using molecular docking technique (Borse *et al.*, 2021) with focus on top 3 Ayurveda herbs - Ashwgandha, Giloy- *Tinospora cordifolia* (Thunb.) Miers. and Satavari (*Asparagus racemosus* Willd.) showed the need for detailed DDI (drug-drug interactions) and HDI (herb-drug interaction) studies. DDI and HDI can be predicted by PK-PD pathways) of particular drug. Cytochrome P450 system (CYP's) are major enzymes that catalyze biotransformation of drugs. CYP1A2, CYP3A4, CYP2C9 and CYP2D6 modulate metabolism of around 80–90% of drugs. *In vitro* studies on human liver microsomes using whole plant extracts of AR, TC, and WS showed no inhibition of the main CYP isoforms. Drug metabolizing enzymes overlap especially among the allopathic drugs, DDIs may be risky. WHO Solidarity trial drugs (Remdesivir; Lopinavir/ Ritonavir; Lopinavir/ Ritonavir with Interferon beta-1a; and Chloroquine or Hydroxychloroquine) are

being metabolized by CYP1A2, CYP3A4, CYP2C9, and/or CYP2D6. The common hypertension drugs (Losartan, Metoprolol, Propranolol, Telmisartan,) and T2DM (Glimepiride, and Pioglitazone) shares the same drug metabolizing enzymes (CYP1A2, CYP3A4, CYP2C9, and CYP2D6). Thus, careful pharmaco-therapeutic management is needed and pharmacokinetic mediated HDI may not occur with the studied *Rasayana* botanicals as no such overlap has been found in these *in-silico* studies and published *in vitro data*.

Some Rasayana drugs are common in diet, and majority households during the pandemic to raise immunity drank spice decoction called "Kadha" in vernacular, comprising spices and Tulsi (Hoy Basil)/ Giloy/ Licorice/ Arjuna described below (*Terminalia arjuna* L.) (Singh *et al.,* 2021). The most important immunomodulatory Indian herbs include the Giloy i.e. heart-shaped moon seed" and Licorice (*Glycyrrhiza glabra* L.) that modulate the response of CD4+ and CD 8+ T cells against viral infections. In silico studies results regarding spice ingredients and COVID-19 virus are re-casted in Table 4 for easy reading (Singh *et al.,* 2021). Similarly, astringent fruit Embelic Myrobylan (*Phyllanthus emblica)* that forms the bulk of the above tonic and is often consumed as pickle or jam or juice in many Indian families enhances the immunity both in vitro and in vivo, especially in natural killer (NK) cell-induced cytotoxic activity (Huabprasert *et al*., 2012). These *Rasayana* herbs can ameliorate various COVID-19 symptoms.

Table 4. COVID-19 & Ayurveda herbs (Rasayana) action (Singh *et al.*, 2021)

A) DIET	**INGREDIENTS**	
Potential target	**Phytoconstituents**	**SPECIES**
a) 3 CL protease	Curcumin	CL
b) High binding affinity to ACE2 protein and main protease (MPro)	Phyllaemblicin G7	PE
	Piperolactam A	PE
B) **HERBAL TONICS**		
Potential target	**Phytoconstituents**	**SPECIES**
a) 3 CL protease	Berberine	TC
	Withanolide I	WS
b) High binding affinity to ACE2 protein and main protease (MPro)	Phyllaemblicin G7	PE
	Withaferin A	WS
	Cordioside and other constituents	TC
c) ACE2–RBD interface	Withanone	WS
	Withanolide A	
d) Spike protein	Phyllaemblicin G7	PE
	Racemoside A, C Asparoside-C,F	AR
	Withaferin	WS
	Withanolide M	WS

SPECIES: AR- *Asparagus racemosus* Willd. (Satavar/ Asparagus), CL- *Curcuma longa* L. (Haldi/ Turmeric), PE- *Phyllanthus emblica* L. ((*Aamlaki*/ Embelic Myrovylan), PL- *Piper longum* L. (Gol Mirch/ Back pepper), TC- *Tinospora cordifolia* (Thunb.) Miers. (Guduchi), WS- *Withania somnifera* (L.) Dunal (Ashwagandha/ Indian Ginseng)

Other 3 key herbs commonly consumed as tonics, often singly in India in fewer yet significant number of families having pro-traditional diet/ lifestyle. These are also found to reduce COVID-19 intensity - 1) *Asparagus racemosus* Willd. (Asparagus), 2) *Tinospora cordifolia* (Thunb.) Miers. (Guduchi), 3) *Withania somnifera* (L.) Dunal (Indian Ginseng), by action on one or more of the following – ACE2–RBD interface, 3 CL protease, Mpro, Nsp 15

endoribonuclease, RBD complex. This explains the basis for the lower COVID-19 fatality in India as depicted in Table 2 (Singh *et al.*, 2021).

Immunity Building Mechanism of Action of Herbs/ Spices

"Rasayanas" i.e. are used to combat the ageing effects, atherosclerosis, cancer, diabetes, rheumatoid arthritis and Parkinson's disease (Kumar *et al.*, 2012). These operate as (a) immune-stimulant, (b) immune-adjuvant, or as (c) immune-suppressant by affecting the effector arm of the immune response. They stimulate phagocytosis, activate macrophages, affect peritoneal macrophages, stimulate lymphoid cells, enhance nonspecific cellular immunity and raise antigen-specific immunoglobulin production, natural killer cell numbers, and reduce chemotherapy-induced leukopenia, and increase circulating total white cell counts and interleukin-2 levels.

Agents activating host defense system against impaired immune response can support the conventional chemotherapy. High cell proliferation makes bone marrow a sensitive target, especially to various cytotoxic drugs. Bone marrow is most affected organ during any immunosuppression therapy. Loss of stem cells and bone marrow's inability to regenerate new blood cells results in thrombocytopenia and leucopenia. Some medicinal plants may stimulate the immune system, (e.g., Ginseng- *Panax ginseng* Meyer, Holy Basil- *Ocimum sanctum* L, Giloy- *Tinospora cordifolia* (Thunb.) Miers., and Arjuna- *Terminalia arjuna* L.), while some suppress the immune response (*Alternanthera tenella* Colla). Alkaloids, glycosides, saponins, flavonoids, coumarins, and sterols i.e secondary metabolites show varying immune-modulating activity.

Ayurveda has listed 24 Rasayana and 68 non Rasayana herbs with high immunomodulatory potential such as *Aconitum heterophyllum* Wall. Ex Royle (Atis) (Doshi *et al.*, 2017) from the anti-malerial supermolecule "Artemissin" yielding species cohort. This study explains that the herbs limit the "ama" i.e. immunologically active complexes generated in intestine due to improper digestion of food causing pathogenesis in various diseases such as ulcerative colitis, rheumatoid arthritis and many liver related ailments. Drugs can influence "ama" in 2 ways:

a. Those, which increase digestion capacity and prevent the formation of "ama" e.g. Ginger,

b. Those, which digest "ama" e.g. Turmeric.

Besides the "ama" concept, many herbs that possess anti-allergic properties are also categorized as "immune-modulators" on the basis of stimulation of T-suppressor cells, e.g. *Piccorrhiza kurrora* Royle ex Benth. (Kutki- vernacular) reportedly affects the sensitivity of guinea pigs to histamine and sympathomimetic amines and also prevents allergen and platelet activating factor that induces the bronchial obstruction. *P. longum* L. is also often used to treat in bronchial asthma.

The immunity action of Ayurveda herbs is explained much before the recent pandemic (Tripathi & Singh, 1999). For instance, Giloy, an important Rasayana drug, is anti-complementary and immune-stimulating, Hepato-protective, antidiabetic, anti-inflammatory and. Syringin (TC-4) inhibited the in vitro immunohaemolysis of antibody coated erythrocytes. Inhibition of the C3-convertase of the classical complement pathway that rises IgG antibodies in the serum, is its caus. Humoral and cell mediated immunity also enhanced dose dependently. Macrophage activation was seen in cordioside (TC-2), cardiofolioside – A (TC-5) and Cordiol (TC-7), that induced phagocytic activity much by activating peritoneal macrophages.

Yastimadhu i.e. Licorice (Glycirrhiza glabra L.), is another important Rasayana drug isimmunostimulative, and accelerates the lymphocytic activation of macrophage and increases leucocyte count [*ibid.*]. Combination of the Rasayana drugs – Amalaki, Vidang and

Atibala (Amalaki compound) in a controlled clinical study has increased immunoglobulin levels in infants significantly greater than that of multivitamin used cases vide studies.

Triterpenes can explain some of these effects. These are secondary metabolites linked to "Saponin" group and comprising 30 carbon atoms formed by the combination of 6 isoprene units, being immunomodulatory (Renda *et al.*, 2022). Different triterpenes are formed by cyclization and oxidation of 2 C_{15} units, squalene, or related acyclic 30-carbon C_{30} precursors. Triterpenes are classified as a) tetracyclic (dammarane, cucurbitane, lanostane and cycloartane types) and b) pentacyclic (oleanane, ursane, lupane, friedelane, hopane, and taraxastane types). Their immunomodulatory properties are much studied- oleanolic acid, glycyrrhizin, glycyrrhetinic acid, pristimerin, ursolic acid, boswellic acid, celastrol, lupeol, betulin, betulinic acid, ganoderic acid, cucumarioside, and astragalosides. Garlic is a famous spice rich in triterpenoids and Organosulfur compound "allicin" and is famous for managing hypertension and heart care (Rajagopal *et al.*, 2020).

Arjuna Herbal Tea – Emerging Superfood and COVID-19 Treatment

A prominent and emerging superfood can be a global herbal tea from India soon is called "Arjun" in Sanskrit and many Indian languages. It is rich in Triterpenes, among other healthy phytochemicals (Dwiwedi & Chopra, 2014). It is a tall, magnificent forest tree with whites, glazed, peeling of bark in stripes, on river banks in south Asia. It is a famous traditional medicine for heart ailments & bone fractures in India in Ayurveda & folk systems. It has comparable antioxidant capacity and total phenol content (TPC) to the famous green tea (*Camellia sinensis* (L.) Kuntze) as evident from Table 5 so can be promoted as health drink, as it is safe for routine consumption. Besides, Arjuna also has substantial health benefits such as reducing hypertension or build muscles.

Arjuna bark boiled in milk is consumed 1-2 times a day, as Arjuna has hot potency while milk has coolant properties to balance it, vide Ayurveda. Moreover, the fats in the milk my enhance polyphenol absorption and improve therapeutic effect as in the case of curcumin, a flavanoid (polyphenol) Turmeric (Aggarwal *et al*., 2011). Arjuna may be avoided with anticoagulant drugs as it is a blood thinner.

Tannins and glycosides present in Arjuna bark are antioxidants that protect the heart muscles and blood vessels against from free radicals. Arjuna also helps in the dilation of the blood vessels and dissolves the plaque to improve blood flow, thus reducing cardiac problems and high blood pressure, palpitations and rapid heartbeat (Haq *et al*., 2012, Shahid *et al*., 2014).

Table 5. Arjuna and Green tea polyphenol & antioxidant capacity comparison

PARAMETER	Arjuna [*ibid.*]	Green tea
Total Phenolic content GAE g/100g	6-11	14-25 (Zhao *et al.*, 2019)
Antioxidant value mg/ml	2.7-7.1	8-13 (Farooq & Sehgal 2018)
Bioactive ingredients	Tannins, Triterpenoid saponin (Arjunic acid etc.)	Tannin, Polyphenols, EGCG

Note: GAE- Gallic acid equivalent #- 148-252 mg/g GAE, EGCG- Epigllocatechin gallate

A study in Chennai, India regarding Oleanane triterpenoids type compounds *viz.*, oleanolic acid, arjunolic acid, arjunolitin, arjunetin in ethanolic bark extract found them as "bio-active" compounds and their structures were elucidated using ^{1}H, ^{13}C NMR, HR-ESIMS, IR (Arumugam *et al.*, 2021). Arjunetin showed significant inhibition of catalase activity & its structurally like current antiviral drugs. Molecular docking studies showed that

it binds to the key targets of SARS-CoV-2 namely, 3CLpro, PLpro, and RdRp) with a higher energy values (3CLpro, −8.4 kcal/mol; PLpro, −7.6 kcal/mol and RdRp, −8.1 kcal/mol) than Lopinavir (3CLpro, −7.2 kcal/mole and PLpro −7.7 kcal/mole) and Remdesivir (RdRp −7.6 kcal/mole). Molecular dynamics simulation studies with 200–500 ns showed that the binding affinity of Arjunetin is higher than Remdesivir in the RNA binding cavity of RdRphence.

A docking study in Delhi had similar findings with PyRx tool (Wanarase *et al.*, 2022). ADME and drug likeness analysis were done using Swiss-ADME and Admetlab web server. Ramachandran plot analysis shows the statistical distribution of the combinations of the backbone dihedral angles ϕ and ψ of the protein. Molecular docking studies show 5 compounds of *T. arjuna*, with potential binding affinity to resist the main protease Mpro by preventing proteolytic cleavage, translation, and replication of virus. ADMET profile and drug likeness prediction showed that, among them Triterpenoid and N-Desmethyl Sildenafil were safe and possess the drug-like properties. Triterpenoid and N-Desmethyl Sildenafil have specific binding affinity and inhibited main protease Mpro as a drug in COVID-19.

The in vitro antithrombotic effects of Arjuna are reported in 20 patients with coronary artery disease (CAD) (Dwiwedi *et al.*, 2022), attributed to the desensitization of platelets and/or transduction mechanisms involved in thrombosis. A randomized controlled clinical trial in diabetic patients mentioned revealed that Arjuna significantly inhibited platelet aggregation. In the CAD patients, 1 -month administration of Arjuna significantly reduced the platelet count. This may have therapeutic significance in preventing post-COVID-19 thrombotic events. As estimated in a randomized controlled clinical trial (n = 105) in CAD patients, Arjuna (500 mg) had antioxidant effect similar to Vitamin E (400 IU).

This preclinical study further substantiates the efficacy of Arjuna as it contains triterpenoids, flavonoids, and glycosides, known to interact with the angiotensin converting enzyme-2 (ACE2), crucial in the SARS-CoV2 infection and in later complications. The *Arjuna* bark extract contains 1.08% quercetin and 0.16% rutin along with β-sitosterol. In the rat model of myocardial ischemia/reperfusion injury-induced arrhythmias, quercetin is proved to exert heart protective effect. *Arjuna* bark extract also contains other polyphenols such as gallic acid, gallocatechin, epigallocatechin, catechin, and epicatechin, and ameliorate the oxidative stress in the post-COVID-19 complications.

Calming of cytokine storms, post COVID-19 recovery is a major concern globally. Arjuna and some other herbs can in principle reduce or avoid such damage, it has been shown in different Indian studies (Gour *et al.*, 2021; Peter *et al.*, 2021). This has promoted Indian scientists to promote chemical extract ingredients from potent herbs as COVID-19 remedy elixir (Ahmed *et al.*, 2020).

COVID-19 Pandemic & Diet

Importance of fruit and vegetable consumption in the pandemic is underlined by the U. K. Biobank (UKB) study where participants (*n* = 37,988) aged 40-70 years at baseline experienced 17% positivity for COVID-19 (Vu *et al.*, 2021). After multivariable adjustment, the odds of COVID-19 positivity was 0.90 when consuming 2–3 cups of coffee/day (vs. <1 cup/day), when consuming vegetables in the third quartile of servings/day (vs. lowest quartile) it was 0.88, and it was 1.14 when consuming fourth quartile servings of processed meats (vs. lowest quartile). The associations were attenuated if further adjusted for COVID-19 exposure but the patterns of associations remained. Processed meat consumption was adversely associated with COVID-19 while coffee & vegetables consumption showed lower incidence of COVID-19.

Similar inverse relation was found globally between COVID-19 intensity and vegetable consumption (Abdulah & Hassan, 2020). The crude infection rate was related to fruits

consumption and calcium and was less under rising beans and legumes consumption. The crude mortality rate was higher with higher consumption of sugar-sweetened beverages but reduced with increasing consumption of fruits, beans and legumes.

Ultra processed foods (UPF) are consumed much in the west and are a big health risk as evident in a Chinese study of COVID-19 (Zhou *et al.,* 2023). Among the UPF proportion (% daily gram intake) in the diet groups, the lowest quartile of had lowest COVID-19 risk, but participants in the 2nd, 3rd, and highest quartiles had higher such risk with the odds ratio (OR) value of 1.03, 1.24 and 1.22 respectively (P for trend < 0.001) after Potential confounders were adjusted. UPF proportions and age groups, education level, body mass index, and comorbidity status were unrelated but BMI accounted for 13.2% of the association. COVID-19 prevalence and mortality is similarly correlated across nations with high immunity suppressant diet (Ghate & Kulkarni, 2022).

Advanced Glycation products (AGE) poses another risk in the western diet with red meat and cooked at high temperature (Luevano-Contreras *et al.,* 2010). AGEs could be implicated in the development of chronic degenerative diseases of aging, such as cardiovascular disease, Alzheimer's disease and with diabetes. Malondialdehyde (MDA) is an indicator of the oxidative stress caused by such AGE products but are limited in the vegetarian diet. A study in southern India had shown that the Lacto vegetarians had 3.76 nmol/ ml Malondialdehyde i.e. nearly 50% of the value for the non-vegetarians 7.29 nRj/g of nmol/ ml (Somannavar & Kodliwadmath, 2011). Conversely, Glutathione peroxide, an antioxidant indicator was higher among the lacto-vegetarians (19.7 RJ/gof Hb) but 30% less among the meat eaters (13.2 RJ/g of Hb) that reflects the oxidative stress. Vitamin A among the non-vegetarians was 14% less than the vegetarians (35.6 ng/dl) and vitamin E was 9% less among the non-vegetarians.

Dietary ingredients such as Rapeseed/ Mustard (*Brassica juncea*) protect from lipidoxidation, a Swedish study showed (Sodergren *et al.*, 2001). Plasma or urinary levels of free 8-iso-prostaglandin F2a, plasma total 8-isoprostaglandin F2a plasma hydroperoxides or plasma MDA did not differ between the rapeseed and control diets. Serum g-tocopherol level was higher after the rapeseed diet than the normal diet ($P < 0.001$), but the serum a-tocopherol concentration and plasma anti oxidative capacity was similar in the 2 diets. The total cholesterol, LDL cholesterol and LDL=HDL ratio were lower after the rapeseed diet than the control diet ($P < 0.001$) but HDL cholesterol and total triglyceride levels did not differ in the 2 diets. Thus, a-linolenic acid rich rapeseed oil-based diet did not affect the degree of lipid peroxidation in plasma and urine than the saturated fat rich diet. Rapeseed oil diet antioxidants may increase circulating concentrations of antioxidants protecting the unsaturated fatty acids. Mustard is common cooking oil in the northern India and may cause less oxidative stress among people.

Many fruits & vegetable (F&V) are considered "superfoods" but their consumption is inadequate in many parts of the world as evidenced by the recent poor immunity observed across the globe. Study in Kolkata metro, India for instance showed that the youth had poor dietary intakes; with 30% not consuming vegetables and 70% ate >3 servings/ day of energy-dense snacks (Rathi *et al.,* 2017). Nearly 45% consumed no fruits and 47% drink > 3 servings of energy-dense beverages. The mean consumption in serves/day of the main food groups varied from 0.88 (SD = 1.36) for pulses and legumes to 6.25 (SD = 7.22) for energy-dense snacks. Thus, healthy eating habits in the in adolescence need to be promoted.

In Europe, 33% persons did not consume any fruit or vegetables daily and only 12% of the population ate the recommended 5 portions daily in 2019 (Anon, 2022c). On average, 55% of the EU population ate 1 and 4 portions of fruit and vegetables daily. The highest daily intake of 5 portions or more was reported in Ireland (33% of the population), the Netherlands (30%), Denmark (23%) and France (20%). Romania had the lowest intake, where only 2% of

the population ate at least 5 portions of F&V, while Bulgaria and Slovenia (both 5%) and Austria (6%) resembled it. Other studies too confirmed low F&V consumption in EU (Stea *et al.*, 2020).

In USA also only 10-12% adults met F&V diet recommendations in 2019 (Lee *et al.*, 2022). Vegetable intake recommendations were met most among adults aged ≥51 years (12.5%) and lowest among adults with low income (6.8%). Mortality was strongly negatively correlated and fruits & vegetable intake (5 potions- 400 g, vide WHO recommendation) in a cohort study in USA (Dong *et al.*, 2022). Similar relation is visible in EU countries vide Table 6 and Figure 2.

Table 6. COVID-19 mortality & fruits-vegetable diet in EU countries

COUNTRY	Veg % people (adequate F&V intake) #	% Fatality*	Cases Total	Mortality**
France	22	0.59	2,37,58,447	2.1
UK	20	0.82	1,99,11,155	2.4
Germany	12	0.71	1,78,43,545	1.5
Turkey		0.66	1,46,23,028	1.1
Italy	11	1.16	1,35,63,466	2.6
Spain	11	0.90	1,12,60,040	2.2
Netherlands	30	0.30	73,27,235	1.3
Poland	9	1.94	58,63,414	3.0
Czechia	8	1.06	37,16,181	3.7
Belgium	17	0.83	36,83,784	2.6
Portugal	16	0.63	33,80,263	2.1
Austria	5	0.46	33,35,900	1.7
Switzerland	20	0.42	31,92,119	1.5
Denmark	25	0.19	28,35,490	0.9
Romania	5	2.30	28,02,848	3.4
Greece	11	0.99	27,08,610	2.6
Sweden	7	0.72	24,72,068	1.8
Serbia	5	0.80	19,47,591	1.8
Hungary	8	2.47	18,20,767	4.7
Slovakia	9	1.18	16,08,668	3.5
Norway	13	0.49	13,68,165	0.3
Ireland	35	0.69	13,65,467	1.3
Solvenia	5	0.36	9,25,939	3.1
Finland	14	0.51	7,82,912	0.5

Source: % of vegetable (adequate) consuming people (Anon 2022c, https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20220104-1)
– This reflects the % of people consuming 5 potions of fruits & vegetables daily, not pure vegetarians
* – % fatality is the % of deaths among the COVID-19 patients
** – mortality is the no. of deaths/1,000 (one thousand) population due to COVID-19
The 24 countries are listed in the decreasing order of no of total cases.
Note: The countries with higher % of people with adequate F&V diet have lower death rate.

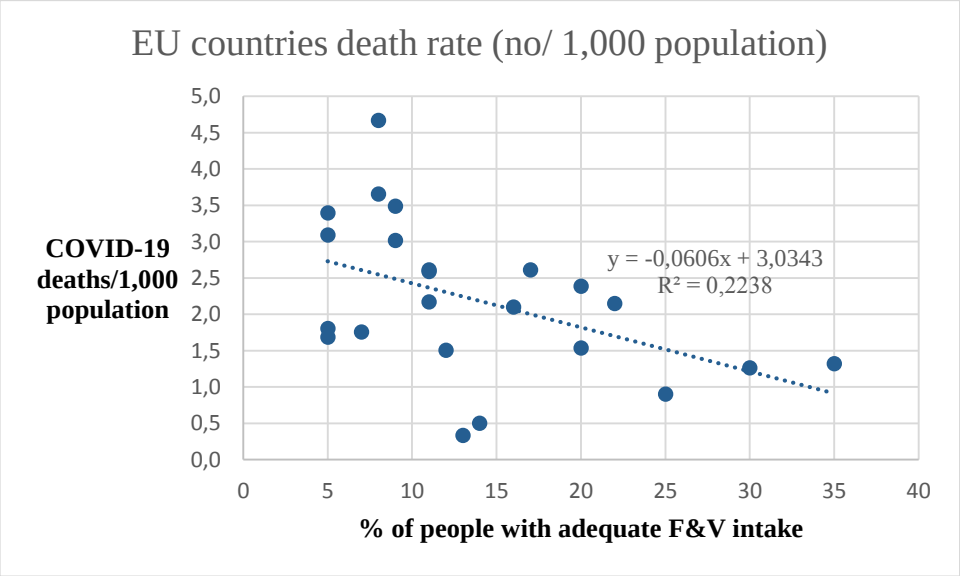

Figure 2. EU countries death rate (no/ 1,000 population) and F&V consumption

CONCLUDING REMARKS

Herbal products' crucial role in immunomodulation to prevent the infection as well as combat the cytokine release storm (CRS) generated during COVID-19 infection is highlighted. To manage COVID-19 damage, flavonoids have been reported to be useful e.g. quercetin, rutin. Spices rich in polyphenols and mainly vegetarian diet, being highly antioxidant may have helped in lower COVID-19 prevalence and mortality in India. Main bioactive ingredients driving this may include flavonoids in Turmeric (Curcumin) and Onion, Coriander (Quercetin), an alkaloid (Piperine) in Black pepper, and Mustard (Allyl isothiocyanate, an organosulfur compound). These act like slow medicine/ adjuvants and help immunity. Other factors like less processed foods, higher vitamin D exposure etc. may have also helped in it. Adjuvant such as lipid is critical for the medicinal effect of polyphenols and they need bio-enhancement due to low bioavailability and black pepper can enhance bioavailability of other spice bioactives.

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CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Abdulah, D. M. & Hassan, A. B. (2020). Relation of Dietary Factors with Infection and Mortality Rates of COVID-19 across the World. *Journal Nutrition, Health & Aging*, *24*, 1011–1018. https://doi.org/10.1007/s12603-020-1434-0.

Aggarwal, B., Prasad, S., Reuter, S., Kannappan, R., Yadav, V.R., Park, B. et al. (2011). Identification of Novel Anti-inflammatory Agents from Ayurvedic Medicine for Prevention of Chronic 20142014Diseases- "Reverse Pharmacology" and "Bedside to Bench" Approach. *Current Drug Targets*, *12*(11), 1595–1653. https://doi.org/10.2174/138945011798109464.

Ahmed, A. K., Albalawi, Y. S., Shora, H. A., Abdelseed, H. K., & Al-Kattan, A. N. (2020). Effects of quadruple therapy: Zinc, quercetin, bromelain and vitamin C on the clinical

outcomes of patients infected with COVID-19. *Res Intl. Journal Endocrinology Diabetes*, *1*(1), 18–21. https://doi.org/10.37179/rijed.000005.

Amrein, K., Scherkl, M., Hoffmann, M. et al. (2020). Vitamin D deficiency 2.0: an update on the current status worldwide. *European Journal Clinical Nutritio*n, *74*, 1498–1513. https://doi.org/10.1038/s41430-020-0558-y.

Anon. (2020a). Prime Ministers statement at World AYUSH conference, Goa. Govt. of India, New Delhi. https://www.pib.gov.in/PressReleseDetail.aspx?PRID=1882565.

Anon. (2022c). How much fruit and vegetables do you eat daily? https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20220104-1

Anon. (2018). The Global Asthma Report. Global Asthma Network. Auckland: 2018. http://globalasthmareport.org/2018/resources/Global_Asthma_Report_2018.pdf

Anon. (2022a) COVID-19 intensity data country wise. www.worldometers.info/coronavirus/

Anon. (2022b). Data on Income category of the countries of the world. The World Bank, Washington. https://databank.worldbank.org/data/download/site-content/CLASS.xlsx.

Anon. (2020b). COVID-19 Advisory. Ayush department, Govt. of India. 2020. www.ayush.gov.in/docs/ayush-Protocol-covid-19.pdf .

Arifian, H., Maharani, R., Megantara, S., Gazzali, A.M., & Muchtaridi, M. (2022). Amino-Acid-Conjugated Natural Compounds: Aims, Designs and Results. *Molecules*, *27*, 7631. https://doi.org/10.3390/molecules27217631,

Arumugam, G. S., Sen, A., Dash, S. S., Mitra, K., Doble, M., Rajaraman, G., & Gummadi, S. N. (2022). Arjunetin as a promising drug candidate against SARS-CoV-2: molecular dynamics simulation studies. *Journal of Biomolecular Structure and Dynamics*, *40*(22), 12358-12379. https://doi.org/10.1080/07391102.2021.1970627.

Bell, L. & Wagstaff, C. (2017). Enhancement of Glucosinolate & Isothiocyanate Profiles In Brassicaceae Crops: Addressing Challenges In Breeding For Cultivation, Storage, and Consumer Related Traits. *Journal Agriculture Food Chemistry*, *65*(43), 9379-9403. https://doi.org/10.1021/acs.jafc.7b03628.

Borse, S., Joshi, M., Saggam, A., Bhat, V., Walia, S., Marathe, A., *et al.* (2021). Ayurveda botanicals in COVID-19 management: An in silico multi-target approach. *PLoS ONE 16*(6), e0248479. https://doi.org/10.1371/journal.pone.0248479.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global Cancer Statistics. Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: Cancer Journal Clinical*, *68*, 394-424. https://doi.org/10.3322/caac.21492.

Carlsen, M. H., Halvorsen, B. L., Holte, K., Bøhn, S. K., Dragland, S., Sampson, L., ... & Blomhoff, R. (2010). The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutrition Journal*, *9*(1). https://doi.org/10.1186/1475-2891-9-3

Chang, J. S., Wang, K. C., Yeh, C. F., Shieh, D. E., & Chiang, L. C. (2013). Fresh ginger (Zingiber officinale) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *Journal of Ethnopharmacology*, *145*(1), 146-151. https://doi.org/10.1016/j.jep.2012.10.043.

Chernukha, I., Kupaeva, N., Kotenkova, E., & Khvostov, D. (2022). Differences in Antioxidant Potential of *Allium cepa* Husk of Red, Yellow, and White Varieties. *Antioxidants*, *11*, 1243. https://doi.org/10.3390/antiox11071243.

Chinnaswamy, S. (2020). SARS-CoV-2 infection in India bucks the trend: Trained innate immunity?. *American Journal of Human Biology*, *33*(6), e23504. https://doi.org/10.1002/ajhb.23504.

Cruz, L., Castaneda-Hernandez, G., & Navarrete, A. (1999). Ingestion of Chilli pepper (*Capsicum annuum*) reduces salicylate bioavailability after oral asprin administration in the rat. *Canadian Journal Physiology Pharmacology*, *77*(6), 441-6.

Daurova, A., Daurov, D., Zhapar, K., Volkov, D., Sapakhova, Z., Shamekova, M. et al. (2022). Improvement of breeding-valuable traits of rapeseed (*Brassica napus)* using mutagenesis. *International Journal Agriculture Biology*, *28*(4), 219–227. https://doi.org/10.17957/IJAB/15.1973.

Dong, W., Li, Y., Bhupathiraju, S., Rosner, B. A., Sun, Q., Giovannucci, E. L. et al. (2021). Fruit and Vegetable Intake and Mortality. Results from 2 Prospective Cohort Studies of US Men and Women and a Meta-Analysis of 26 Cohort Studies. *Circulation*, *143*(17), 1642-1654. https://doi.org/10.1161/CIRCULATIONAHA.120.048996

Doshi, G. M., Une, H. D., & Shanbhag, P. P. (2013). Rasayans and non-rasayans herbs: Future immunodrug - Targets. *Pharmacognosy Review*, *7*, 92-6. https://doi.org/10.4103/0973-7847.120506.

Dwivedi, S. & Chopra, D. (2014). Revisiting *Terminalia arjuna* – An ancient cardiovascular drug. *Journal Traditional Complementary Medicine*, *4*(4), 224–231. https://doi.org/10.4103/2225-4110.139103

Dwivedi, S., Sharma, V., & Patil, C. R. (2022). Can We Use Terminalia Arjuna (Roxb.) Wight and Arn in Place of Novel Oral Anticoagulants (NOACs) in Post-COVID-19 Cardiac Conditions? *Journal Pharmacology Pharmacognosy*, *13*(1), 95-96. https://doi.org/10.1177/0976500X221080202

Eapen, J. T. (2021). Polyphenols in Matily Herbal & Spices Boosts Antibodies in an Elderly Following COVID 19 Infections – A Case Study. *International Journal Medical Science Diagnosis Research*, *6*(1), 20-31.

Elsayed, Y. N. & Khan, A. (2020). Immunity-Boosting Spices and the Novel Coronavirus. ACS *Chemical Neuroscience*, *11*(12), 1696-1698. https://doi.org/10.1021/acschemneuro.0c00239

Escobar, L.E., Molina-Cruz, A. & Barillas-Mury, C. (2020). BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proceedings National Academy Sciences*, *117*(30), 17720-17726. https://doi.org/10.1073/pnas.2008410117

Farooq, S. & Sehgal, A. (2018). Antioxidant Activity of Different Forms of Green Tea: Loose Leaf, Bagged and Matcha. *Current Research Nutrition Food Science*, *6*(1). http://dx.doi.org/10.12944/CRNFSJ.6.1.04

Gadgil, M., Rao, P. R. S., Utkarsh, G., Pramod, P., & Chhatre, A. (2000). New meanings for old knowledge: the people's biodiversity registers program. *Ecological applications*, *10*(5), 1307-1317.

Ghate, U. & Kulkarni, H. (2022). Packed Foods Related to COVID-19. *Journal Ecology & Natural Resources*, *6*(4), 000309. https://doi.org/10.23880/jenr-16000309

Ghate, U., Kulkarni, H., & Arunachalam, A. (2019). Spices in the eastern Indian laterite soil have more polyphenols? *Indian Journal Hill Farming*, *32*(2), 236-238. http://www.kiran.nic.in/pdf/IJHF/Vol_32_2/8.%20Final.pdf

Ghate, U. & Wele, A. (2022). Globalization of AYUSH Products: Status, Challenges and suggestions for Growth. *Traditional Medicine Review*, *1*(2), 21-34.

Ghate, U. & Kulkarni, H. (2021). Polyphenols, Spices and Vegetarian Diet for Immunity and Anti-Inflammatory Drug Design. In L. Q. Zepka, T. C. Nascimento, & E. Jacob Lopes (Eds), *Bioactive Compounds–Biosynthesis, Characterization and Applications* (pp. 63-76). London: Intechopen. https://doi.org/10.5772/intechopen.97661

Goetz, K., Hinz, A., Steinhäuser, J., & Von Rath, U. (2020). Use of mustard seed footbaths for respiratory tract infections: A pilot study. *Evidence-Based Complementary and Alternative Medicine, 2020,* 5648560.

Gour, A., Manhas, D., Bag, S., Gaorain, B., & Nandi, U. (2021). Flavonoids as potential phytotherapeutics to combat cytokine storm in SARS-CoV-2. *Phytotherapy Research, 35*(8), 4258–4283. https://doi.org/10.1002/ptr.7092

Griffin, G., Hewison, M., Hopkin, J., Kenny, R., Quinton, R. et al. (2020). Vitamin D and COVID-19: evidence and recommendations for supplementation. *Royal Society open science*, *7*(12), 201912. https://doi.org/10.1098/rsos.201912

Guijarro-Real, C., Plazas, M., Rodríguez-Burruezo, A., Prohens, J., & Fita, A. (2021). Potential In Vitro Inhibition of Selected Plant Extracts against SARS-CoV-2 Chymotripsin-Like Protease ($3CL^{Pro}$) Activity. *Foods*, *10*(7), 1503. https://doi.org/10.3390/foods10071503

Haq, M., Huque, M., Chaudhury, A.R., et al. (2012). Cardiotonic effects of *Terminalia arjuna* extracts on guinea pig heart in vitro. *Bangladesh Journal Pharmacology*, *7*, 164-168. https://doi.org/10.3329/bjp.v7i3.11034

Huabprasert, S., Kasetsinsombat, K., Kangsadalampai, K., et al. (2012). The *Phyllanthus emblica* L. infusion carries immunostimulatory activity in a mouse model. *Journal Medical Association Thailand*, *95*(2), S75–S82.

Kala, C.P., Dhyani, P.P., & Sajwan, B.S. (2006). Developing the medicinal plants sector in northern India: challenges and opportunities. *Journal Ethnobiology Ethnomedicine*, *2*, 32. https://doi.org/10.1186/1746-4269-2-32

Kesarwani, K. & Gupta, R. (2013). Bioavailability enhancers of herbal origin: An overview. *Asian Pacific Journal Tropical Biomedicine*, *3*(4), 253–266. https://doi.org/10.1016/S2221-1691(13)60060-X.

Kiviranta, J., Huovinen, K., & Hiltunen, P. (1988). Variation of phenolics in onion. *Acta Pharmaceutica Fennica*, *91*, 67-72.

Kumar, D., Arya, V., Kaur, R., Bhat, Z. A., Gupta, V. K., & Kumar, V. (2012). A review of immunomodulators in the Indian traditional health care system. *Journal Microbiology, Immunology, Infecttions*, *45*, 165e184, 165-184. https://doi.org/10.1016/j.jmii.2011.09.030

Kumar, P. & Chander, B. (2020). COVID 19 mortality: Probable role of microbiome to explain disparity. *Medical Hypotheses*, *144*, 110209. https://doi.org/10.1016/j.mehy.2020.110209

Kunnumakkara, A. B., Rana, V., Parama, D., Banik, K., Girisa, S., Henamayee, S., ... & Aggarwal, B. B. (2021). COVID-19, cytokines, inflammation, and spices: How are they related?. *Life Sciences*, *284*, 119201.

Kunnumakkara, A.B., Bordoloi, D., Padmavathi, G., Monisha, J., Roy, N.K., Prasad, S. et al. (2017). Curcumin, the golden nutraceutical: multi-targeting for multiple chronic diseases. *Brazilian Journal Pharmacology*, *174*(11), 1325–48. https://doi.org/10.1111/bph.13621

Lee, S. H., Moore, L. V., Park, S., Harris, D. M., & Blanck, H. M. (2022). Adults meeting fruit and vegetable intake recommendations—United States, 2019. *Morbidity and Mortality Weekly Report*, *71*(1), 1-9. https://doi.org/10.15585/mmwr.mm7101a1

Luevano-Contreras, C. & Chapman-Novakofski, K. (2010). Dietary Advanced Glycation End Products and Aging. *Nutrients*, *2*(12), 1247–1265. https://doi.org/10.3390/nu13082638.

Mair, E., Liu, R., Atanasov, A. G., Shmidtke, M., Dirsch, V. M., & Rollinger, J. M. (2016). Antiviral and anti-proliferative actions of piperamides in black pepper. *Planta Medica.*, *81*(S01), S1-S381. https://doi.org/10.1055/s-0036-1596830

Marini, E., Magi, G., Mingoia, M., Pugnaloni, A., & Facinelli, B. (2015). Antimicrobial, Anti-Virulence of Capsaicin on Erythromycin-Resistant, Cell-Invasive Group A Streptococci. *Frontiers. Microbiology*, *6*, 1281. https://doi.org/10.3389/fmicb.2015.01281

Negi, S., Bhatt, S., & Bala, L. (2021). Prevention of SARS-CoV-2 Infection with Antioxidants and Antiinflammatory Action of Indian Spices: Light at the End of the Tunnel. *Journal Clinical Diagnostic Research*, *15*(8), OE01-OE07. https://doi.org/10.7860/JCDR/2021/49530.15245

Paterson, J. R., Srivastava, R., Baxter, G. J., Graham, A. B., & Lawrence, J. R. (2006). Salicylic Acid Content of Spices and its Implications. *Journal Agriculture Food Chemistry*, *54*(8), 2891-2896. https://doi.org/10.1021/jf058158w

Patil, B. S., Pike, L. M., & Yoo, K. S. (1995). Variation in the Quercetin Content in Different Colored Onions *(Allium cepa* L.) *Journal American Society Horticulture Sciences*, *120*(6), 909-913.

Pawar, K. S., Mastud, R. N., Pawar, S. K., Pawar, S. S., Bhoite, R. R., Kulkarni, M. V. & Deshpande, A. R. (2021). Oral Curcumin With Piperine as Adjuvant Therapy for the Treatment of COVID-19: A Randomized Clinical Trial. *Frontiers Pharmacology*, *12*, 669362. https://doi.org/10.3389/fphar.2021.669362

Peter, A. E., Sandeep, B. V., Rao, B. G., & Kalpana, V. L. (2021). Calming the storm: natural immunosuppressants as adjuvants to target the cytokine storm in COVID-19. *Frontiers in Pharmacology*, *11*, 583777. https://doi.org/10.3389/fphar.2020.583777

Rajagopal, K., Byran, G., Jupudi, S., & Vadivelan, R. (2020). Activity of phytochemical constituents of black pepper, ginger, and garlic against coronavirus (COVID-19): an in silico approach. *International Journal of Health Allied Sciences*, *9*(5), 43-50. https://doi.org/10.4103/ijhas.IJHAS_55_20

Rathi, N., Riddell, L., & Worsley, A. (2017). Food consumption patterns of adolescents aged 14–16 years in Kolkata, India. *Nutrition Journal*, *16*, 50. https://doi.org/10.1186/s12937-017-0272-3.

Renda, G., Gökkaya, İ., & Şöhretoğlu, D. (2021). Immunomodulatory properties of triterpenes. *Phytochemistry Reviews*, *21*(2), 537–563. https://doi.org/10.1007/s11101-021-09785-x

Roberts, N., Brown, R. E., Buja, L. M., & Weerasinghe, P. (2020). Molecular mechanisms of curcumin in COVID-19 treatment and prevention: a global health perspective. *Medical Research Archives*, *8*(10), 22. https://doi.org/10.18103/mra.v8i10.2248

Salazar, C. B., Spencer, P., Mohamad, K., Jabeen, A., Al Abdulmonem, W., & Fernández, N. (2022). Future pandemics might be caused by bacteria and not viruses: Recent advances in medical preventive practice. *International Journal of Health Sciences*, *16*(3), 1-3.

Salehi, B., Machin, L., Monzote, L., Sharifi-Rad, J., Ezzat, S. M., Salem, M. A., ... & Cho, W. C. (2020). Therapeutic potential of quercetin: New insights and perspectives for

human health. *ACS Omega*, *5*(20), 11849-11872. https://doi.org/10.1021/acsomega.0c01818

Shahid Chatha, S. A., Hussain, A. I., Asad, R., Majeed, M., & Aslam, N. (2014). Bioactive components and antioxidant properties of *Terminalia arjuna* L. Extracts. *Journal Food Processing Technology*, *5*(2), 298. https://doi.org/10.4172/2157-7110.1000298

Shahidi, F., & Hossain, A. (2018). Bioactives in spices, and spice oleoresins: Phytochemicals and their beneficial effects in food preservation and health promotion. *Journal of Food Bioactives*, *3*, 8-75. https://doi.org/10.31665/JFB.2018.3149

Sharma, L. (2020). Immunomodulatory Effect and Supportive Role of Traditional Herbs, Spices and Nutrients in Management of COVID- 19. *Journal Peer Scientist*, *3*(2), 8. https://doi.org/10.5281/zenodo.4019532

Singh, N. A., Kumar, P., Jyoti, & Kumar, N. (2021). Spices and herbs: potential antiviral preventives and immunity boosters during COVID-19. *Phytotherapy Research*, *35*(5), 2745-2757. https://doi.org/10.1002/ptr.7019

Singh, R., Goel, S., Bourgeade, Aleva, L., & Tewari, D. (2021). Ayurveda *Rasayana* as antivirals and immunomodulators: potential applications in COVID-19. *Environmental Science Pollution Research International*, *28*(40), 55925–55951. https://doi.org/10.1007/s11356-021-16280-5

Slimestad, R., Fossen, T., & Vågen, I. M. (2007). Onions: a source of unique dietary flavonoids. *Journal of Agricultural and Food Chemistry*, *55*(25), 10067-10080. https://doi.org/10.1021/jf0712503

Södergren, E., Gustafsson, I. B., Basu, S., Nourooz-Zadeh, J., Nälsén, C., Turpeinen, A., ... & Vessby, B. (2001). A diet containing rapeseed oil-based fats does not increase lipid peroxidation in humans when compared to a diet rich in saturated fatty acids. *European Journal of Clinical Nutrition*, *55*(11), 922-931.

Somannavar, M. S. & Kodliwadmath, M. V. (2011). Correlation between oxidative stress and antioxidant defence in south Indian urban vegetarians and non-vegetarians. *European Review for Medical Pharmacological Science*, *16*, 351-354.

Stea, T. H., Nordheim, O., Bere, E., Stornes, P., & Eikemo, T. A. (2020). Fruit and vegetable consumption in Europe according to gender, educational attainment and regional affiliation—A cross-sectional study in 21 European countries. *PLoS One*, *15*(5), e0232521. https://doi.org/10.1371/journal.pone.0232521

Tripathi, J. S. & Singh, R. H. (1999). The Concept and Practice of Immunomodulation in Ayurveda and the Role of Rasayanas as Immunomodulators. *Ancient Science of Life*, *XIX*(1&2), 59-63.

Tripathi, A. K., Ray, A. K., & Mishra, S. K. (2022). Molecular and pharmacological aspects of piperine as a potential molecule for disease prevention and management: evidence from clinical trials. *Beni-Suef University Journal of Basic and Applied Sciences*, *11*(1), 16. https://doi.org/10.1186/s43088-022-00196-1

Upadhyay, R. K. (2017). Tulsi: A holy plant with high medicinal and therapeutic value. *International Journal Green Pharmacy*, *11*(S1), 13. https://doi.org/10.22377/ijgp.v11i01.869

Ventola, C. L. (2010). Current Issues Regarding Complementary and Alternative Medicine (CAM) in the United States. *Pharmacy and Therapeutics*, *35*(8), 461–468.

Vu, T. H. T., Rydland, K. J., Achenbach, C. J., Van Horn, L., & Cornelis, M. C. (2021). Dietary behaviors and incident COVID-19 in the UK Biobank. *Nutrients*, *13*(6), 2114. https://doi.org/10.3390/nu13062114

Wanarase, S., Chavan, S., & Sharm, S. (2022). A Molecular Docking Study: Targeting Covid-19 (Sars-Cov-2) Main Protease Using Active Phytocompounds from *Terminalia Arjuna*. *Innovare Journal Medical Science*, *10*(5), 9-14. http://dx.doi.org/10.22159/ijms.2022v10i5.46122.

WHO. (2019). Global report on traditional and complementary medicine. World Health Organization, Geneva.

Zhan, G., Yang, F., Zhang, L., & Wang, H. (2022). The Relationship between Mustard Import and COVID-19 Deaths: A Workflow with Cross-Country Text Mining. *Healthcare (Basel)*, *10*(10), 2071. https://doi.org/10.3390/healthcare10102071.

Zhang, L., Jackson, C. B., Mou, H., Ojha, A., Peng, H., Quinlan, B. D., ... & Choe, H. (2020). SARS-CoV-2 spike-protein D614G mutation increases virion spike density and infectivity. *Nature Communications*, *11*(1), 6013. https://doi.org/10.1038/s41467-020-19808-4

Zhao, C. N., Tang, G. Y., Cao, S. Y., Xu, X. Y., Gan, R. Y., Liu, Q., ... & Li, H. B. (2019). Phenolic profiles and antioxidant activities of 30 tea infusions from green, black, oolong, white, yellow and dark teas. *Antioxidants*, *8*(7), 215. https://doi.org/10.1002/mnfr.201000641

Zhou, L., Li, H., Zhang, S., Yang, H., Ma, Y., & Wang, Y. (2023). Impact of ultra-processed food intake on the risk of COVID-19: A prospective cohort study. *European Journal of Nutrition*, *62*(1), 275-287. https://doi.org/10.1007/s00394-022-02982-0.