Chapter

Polyphenols, Spices and Vegetarian Diet for Immunity and Anti-Inflammatory Drug Design

Utkarsh Ghate and Hema Kulkarni

Abstract

Much lower COVID-19 incidence and mortality in India compared to the Europe and northern America may relate to higher immunity possibly due to the low consumption of fast/packed food, liquour, tobacco, meat, HFSS- high fat, salt, sugar, besides higher exposure and a key blood protein. Indian spice intake is also double the world average and healthy cooking oil use such as Mustard, and may also explain it. Inflammation is the foundation for many ailments and challenges the immunity and vital in non-communicable ailments are at the centre stage in an aeing world. Polypehnols are crucial anti-inflammatory chemicals from spices that can for wellbeing and reduce adverse drug rections. We show this using Arthritis- a chronic auto-immune disorder, with the hlep of pharmacokinetic studies. Molecular Docking study was performed on the key bioactive compounds of important spices regarding COX2 active site (PDB ID 5IKR). Piperine in Black Pepper had most stability (Black Pepper, −9.99 Kcal/mol) followed by 'Apigenin' (Coriander, −9.63), and 'Curcumin' (Turmeric, −8.66) like quercetin in literature, and higher than the methotrexate (−8.6), the standard drug. Hence, their synergistic combination in fat medium such as clarified butter can lead the future drug design.

Keywords: Polyphenols, immunity, health, spice, Corona, pharmacokinetic, inflammatory, arthritis

1. Introduction

Spices and herbs have been the key to the health security of the oriental world, besides in western world also until the last century. Polyphenols such as flavanoids are aromatic organic compounds having many health benefits being highly antioxidant in nature [1]. These are vital in preventing chronic or non communicable diseases (NCD) also called as "lifestyle ailments" that are common in the western world [2] and the elderly (over 60 years of age), whose share in the world population is growing rapidly, from 10 to 20% of the total [3].

Inflammation and immunity are most important concepts in medicine today, as cause and remedy respectively [4]. Inflammation is the chief mediator behind chronic or lifestyle ailments prevalent today such as heart disease, cancer, diabetes and blood pressure triggering vigorous research on anti-inflammatory and/or immunity booster phytochemicals, for safety and efficacy (*ibid.*).

Antioxidants are able to reduce oxidative damage to the tissues and protect or restore immunity & health. Vegetarian diet especially fruits, vegetables, pulses are

rich in antioxidants, including polyphenols. Spices are among the richest in these, and are anti-inflammatory. Thus, they can be useful to manage immunity disorders such as COVID-19 and Arthritis, an auto-immune disorder of the elderly.

Adverse drug reaction (ADR) is another major concern that spice/herbal medicines can reduce in principle and as experienced, leading to their growing global demand. ADR affects about 5–10% of the patients globally and can cause sever damage/expenses [5]. As spices are permitted food ingredients globally, ADR risk is low.

2. Covid-19 and vegetarian, spice diet relation

The COVID-19 burden cross top 10 infected countries (dt. 28 Feb. 2021) is shown in the **Table 1** and India is the 2nd most infected after USA but its no. of cases (incidence) and per million (7,990) and deaths (113) is the lowest. It is only 16% of the average (47,000/ 1 million) of the other 9 leading countries incidence and 10% of the death rate (1,110/1 million). This makes it worth studying.

2.1 Immunity Buster foods

It is known that the Immunity is compromised by the higher consumption fast/packed foods, refined cards, intoxicants, higher salt, sugar, fat etc. We find the immunity stress foods consumed in 2–30 times in EU/USA (average 9 times intake) than India, as seen in **Tables 2** and **3**, **Figure 1**.

2.2 Immunity booster foods

Indian spice consumption, rich in polyphenols, is 2 times higher (2.07 kg/head/year, **Table 4** and **Figure 2**) than the global average (1.01 kg/head/year) [7] or USA [8]. Cancer incidence (89 per 0.1 million) in India is 50% of the global average (197) 25% of the EU (363) or USA (387), indicating better immunity [9], possibly due to the higher spice consumption. Asthama incidence, a major respiratory ailment and immunity indicator is similarly low in India with below 10% population affected but higher levels in the European nations- 20 to 25% [10].

Country	Total Cases	Total Deaths	Tot Cases/1 M pop	Deaths/1 M pop
World	114,468,838	2,539,109	14,685	325.7
1. USA	29,202,966	524,670	87,886	1,579
2. India	11,097,134	157,092	7,990	113
3. Brazil	10,517,232	254,263	49,248	1,191
4. Russia	4,246,079	86,122	29,088	590
5. UK	4,170,519	122,705	61,222	1,801
6. France	3,736,016	86,332	57,153	1,321
7. Spain	3,188,553	69,142	68,180	1,478
8. Italy	2,907,825	97,507	48,140	1,614
9. Turkey	2,693,164	28,503	31,708	336
10. Germany	2,444,303	70,608	29,112	841

Source- https://www.worldometers.info/coronavirus/ dt. 28 Feb. 2021.

Table 1.
COVID-19 Incidence and death rate in top 10 countries.

Component	Unit	Ind	West	Ratio
1. Alcohol	Lit/ yr	5	10	2
2. Cigarettes	no.s	117	1400	9
3. Sugar	Kg/yr	19	35	2
5. Meat	Kg/yr	5	88	17
6. Fats	Gram/day	45	145	3
7. Salt	Gram/day	10	34	3
8. Refined carbohydrates kg	Kg/yr.	1.5	50	30
9. Packed foods	%	<5	45	10

Table 2.
Immunity Buster Foods Intake Globe per capita/yr. [2].

Item	Developing	% Share	Industrial	% share
Meat	369	17	958	35
Sugar	170	8	328	12
Pulses	99	5	37	1
Tubers	154	7	112	4
veg. Oil	239	11	494	18
Wheat	457	21	627	23
Rice	655	31	153	6
Total	2143		2709	

Table 3.
Various food items share in Calorie intake (Kcal/day/head) [6].

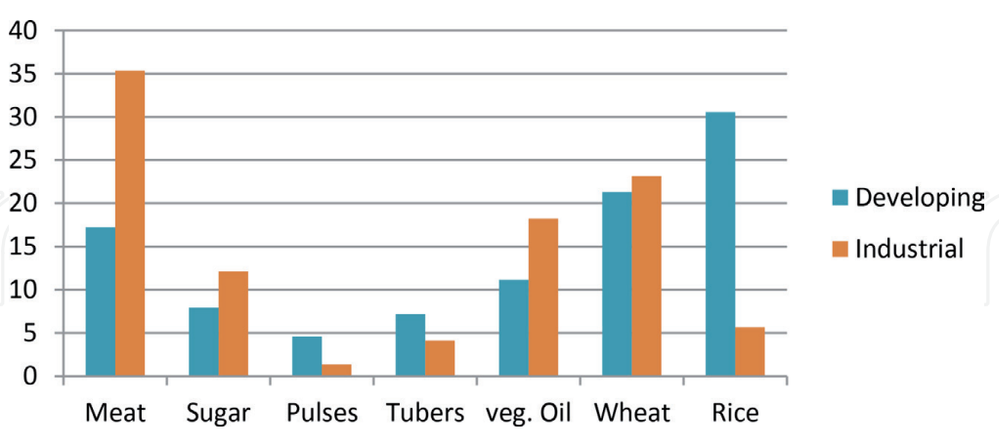

Figure 1.
Food items % in Calorie intake- nations.

However, the spice consumption in India varies greatly across states and economic strata or ethnicity and has changed over times much. Chilli for instance, has replaced black paper, common earlier for adding pungent flavor and changed the world history as European discovered India for the later. The former has no antiviral report [11] while the later is an effective antiviral [12]. Similarly, Chilli is consumed more in northern India while Black Pepper in southern India- its main producer region- and this region also shows lowest fatality rate in India- 1%. Chilli comprises nearly 20% of the 5 gram/day/head spices consumed, and Turmeric, Ginger,

Parameter- region	India [7]	USA [8]	Ratio Rest/India
Spice intake kg/head/year	1	0.6	0.6
Cancer prevalence [9]	89	363	4

Table 4.
Spice Intake & Cancer incidence- India & the world.

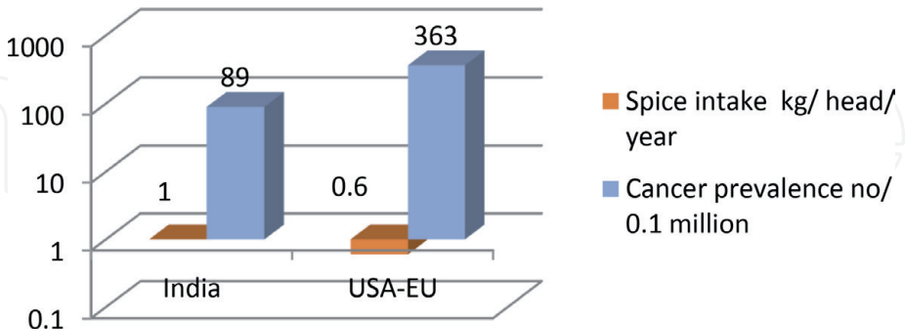

Figure 2.
Spice intake & Cancer Incidence (Note- the Y axis is in the log scale so the world and India incidence is less distinct).

Mustard, Coriander, Cumin are nearly equal, the 5 adding to 80% of the spices consumed on average [7]. More potent antiviral spices (except Ginger & Turmeric) are consumed to lesser extent viz. Cinnamon, Clove and Garlic. The potential of spice bioactive agents as possible COVID-19 remedy or relief is enlisted in **Table 5**.

Scientists have postulated other hypotheses to explain the much lower COVID-19 prevalence and mortality in India/Asia than in the Europe & America, such as the hygiene/exposure [25] and genetics [26], but the role of diet is also mentioned in both prevention and treatment with immunity focus [27]. Spices are found to be important preventive agents and immunity guards in case of the corona, based on data from 163 countries by German scientists [28].

Spices can be important immunity booster due to their bioactive compounds known to be healthy [29, 30]. They may be suppressing the inflammatory pathways

Priority	Ingredient	Effect
1. Coriander	Quercetin	Attachment, endocytosis, cell fusion [13, 14]
2. Ginger	Gingerol	Secrete IFN-β t, inhibits initiation of virus - reduces HRSV-induced plaque [15, 16]
3. Turmeric	Curcumin	Anti-inflammatory, used in rhinitis [17]
4. Pepper, Black	Piperine	Anti-proliferative activity- in vascular smooth muscle cells [18]
Ancillary		
1. Camphor	Imine	1,7,7-trimethylbicyclo [2.2.1] heptanes2-ylidene [19]
2. Cumin	EHP [1-(2-Ethyl,6-Heptyl) Phenol]	Vero cell membrane and/ or HSV-1 envelope [20]
3. Clove	Essential oil, Eugenol	Enveloped virus- HSV-1 and Newcastle [21]
4. Garlic, Onion	Allicin	Block multiplication [22]
5. Tulsi (Holy Basil)	Terpenoid, polyphenols	Non- neuraminidase inhibition [23, 24]

Table 5.
Spices with scope of COVID-19 immunity/cure.

NF-κB and STAT3 [31]. Flavonoids inhibit biosynthesis of prostaglandins (the end products of the COX and lipoxygenase pathways), which acts as a secondary messengers and are involved in various immunologic responses [32]. We illustrate below the scope of use of bioactives from spices to treat Arthritis, a common auto-immune disease with no sure modern cure yet, as drug design example to integrate the traditional wisdom with modern science and technology. But we present some other correlates of Corona intensity and mortality before that in **Table 6**.

Table 6 shows that the corona intensity (no. of cases/ million) is strongly (r = 0.7) correlated with the income per capita and even strongly (r = 0.75) with literacy. The lower corona burden in India and its poorer states may also be because the poorer, illiterate people of states such as U. P., Bihar have stronger immunity, despite higher population density. For, they mainly eat natural foods, with very low amount of packed food, bottled water so low HFSS intake. Hence, the lesser Covid-19 intensity in North & eastern India. Corona is mainly rich countries & people's ailment [33]. Lac of hygiene & exposure to microbes in the slums etc. makes people resistant to microbes, it is said [34]. Migrations improve immunity, is another hypothesis [35]. Mustard oil, common in northern India is antiviral & SARS inhibitor [36], unlike Groundnut in western India, which is an allergen. Lastly, Asians got a protein D614 mutation, making them stronger than the Europeans [37]. These 5 reasons may explain the trend besides Govt. advisory on spice decoction ("Kadha" in Hindi- https://pib.gov.in/PressReleseDetailm.aspx?PRID=1609524).

Its rationale and working mechanism is also explained by scientists [38].

2.3 Spices and herbs- global resurgence

Scientists from Russia & USA describe the health benefits of spices due to their bioactive ingredients & antioxidant nature [39]. They say rosamarinic acid content from the Mint family as beneficial (Oregano- 2,562 mg/100 gm dry weight, Sage- 2,186, Mint- 1908, Sweet Basil- 1,086, & Thyme- 681). Aromatic and medicinal herbs or spices such as these and Parsley, Coriander, Onion, Cumin, Cinnamon, Bay etc. (except Chilli) protect human health due to flavanoid content e.g. Quercetin, Luteolin, Rutin, Apigenin, Myicetin. They indicate that the the herbs are found useful in treating the cancers below-

a. Turmeric- Rectal, oral, head, neck, Leukemia;

b. Saffron- Skin, rectal, hepatic,

c. Garlic- prostate, colon,

d. Onion- Gastric,

e. Mustard- Rectal, Bladder,

f. Bayleaf- melanoma.

They also mention the spices as having therapeutic effects below

1. Cardiovascular- garlic, Turmeric, Ginger

2. Neuro-degenrative- Mint, Onion

3. Antidiabetic- Cinnamon, Bayleaf, Fenugreek, Mustard

State	Popu-lation Million	Popu-lation Density[@]	Corona cases nos.	Corona – Deaths Nos.	Corona Cases/ million	Corona Fatality %[**]	Income[*]	Literacy[#]
Kerala	33	859	1111897	4539	33694	0.41	54	94
Delhi	25	7400	652742	10978	26110	1.68	111	86
Maharashtra	112	365	2600833	53795	23222	2.07	62	82
Andhra	49	303	895879	7201	18283	0.80	44	67
Karnataka	61	319	978478	12471	16041	1.27	48	75
Tamil Nadu	72	555	873219	12641	12128	1.45	54	87
West Bengal	91	1029	583839	10322	6416	1.77	35	76
Gujarat	60	308	298,596	4484	4977	1.50	55	78
Rajasthan	68	200	329595	2811	4847	0.85	31	66
M.P.	76	236	286407	3947	3769	1.38	25	69
Ttar Pradesh	199	828	610273	8783	3067	1.44	20	67
Bihar	103	1102	264604	1571	2569	0.59	13	62
Total	[***]949		[****]9486362					
Correlation coefficient				0.38	–0.07	0.71	0.76	
Correlation between				Cases-Populn. Density	Fatality-Case density	Case density- Income	Case density- literacy	

[@]no. k/ sq. km.
[***]70% of India.
[**]80% of India.
[#]2011 census data.
[*]Rs. K/head/yr- ref. RBI, 2020.
[****](deaths/ cases), M.P.- Madhya Pradesh Ref.- https://www.mohfw.gov.in/, Dt. 28-03-2021.

Table 6.
Corona intensity & socio-economic correlates across Indian states.

4. Gastrointestinal- Black Pepper, Bayleaf

5. Hypertension- Cardamom, Cinnamom,

6. Hepatic- Caraway, cardamom,

7. Endocrine- Ginger, Turmeric,

8. Obesity- Saffron, Turmeric,

9. Renal- garlic, Fennel, Ginger,

10. Alcohol abuse- Thyme, Ginger

Due to the efficacy, safety and sentiments, herbal medicines top the complimentary & alternative medicine (CAM) treatements becoming popular globally recently. The amount of money spent on CAM treatments in the U.S. has skyrocketed in recent years. As per an 2007 survey, Americans spent $33.9 billion out of pocket on CAM therapies that year [40]. About $22 billion was spent on natural products, instructional classes, and materials. Dietary supplements accounted for $14.8 billion of this amount, an expenditure equal to about 1/3rd of out-of-pocket spending or prescription drugs. The remaining $11.9 billion was spent on an estimated 354 million visits to CAM practitioners (acupuncturists, massage therapists, or chiropractors), an amount equal to about 25% of out-of-pocket costs for visits to conventional doctors. The following 10 species (3 spices, 4 herbs) prevail [40]

a. *Echinacea- 41%*,

b. Ginseng- 24%,

c. *Gingko biloba- 21%*,

d. Garlic - 10%,

e. St. John's wort- 12%,

f. Glucosamine- 12%,

g. Peppermint- 12%,

h. Fish oil/omega-3-10%,

i. Ginger - 10%,

j. Soy - 9%.

The main ailments by frequency referred to the CAM practitioners are

1. Back pain- 17%,

2. Neck pain- 6%,

3. Joint pain- 5%,

4. Arthritis- 3.5%,

5. Anxiety- 2.8%,

6. Cholesterol- 2.1%,

7. Head or chest cold- 2%,

8. Other musculoskeletal- 1.8%,

9. Severe headache or migraine- 1.6%,

10. Insomnia- 1.4%.

Reasons for the Increased Use of CAM and Dietary Supplements are

a. the increased availability of information on the Internet

b. increased contact with other cultures that traditionally use CAM.

c. Renewing d interest in formerly countercultural ideologies, such as environmentalism.

d. the perception that CAM is easier to understand, safer, and less expensive than conventional medications.

e. distrust of and frustration with the health care system.

f. a growing recognition that many factors contribute to health and well-being.

With the growing use of the herbal medicines, safety concern is emerging due to the issues such as adulteration, quality and adverse reaction [41]. Hence, World Health Organization (WHO), devised a Traditional Medicine New Strategy (2006–2013) with 3 key health priorities [42], as most countries have traditional/ herbal medicine policy to mainstream it

a. mental health,

b. non-communicable diseases and

c. universal health coverage.

Nevertheless, spices and herbs have great potential in future as depicted below with in the example of an anti-inflammatory drug design excercise.

3. Arthritis drug design

There are globally 1.3 billion cases of musculoskeletal disorders and over 121,000 deaths from such disorders, as well as nearly 139 million disability-adjusted life years, or the number of years lost due to ill-health, disability or early death [43]. Globally, the proportion cases in are led by the low back pain (37%); followed by "other"

(21%); osteoarthritis (19%); neck pain (18.4%); gout (2.6%); and rheumatoid arthritis (1.3%). These proportions changed little from 1990. Surgery and the NSAID- Non steroidal anti-inflammatory drugs- are costly and cause adverse effects such as gastric and cardiovascular issues. The herbal medicines are perhaps effective and in growing demand and even exported much, as dietary supplements that are common globally and many having positive outcomes at least in the short term [44, 45]. But herbs they use are and are often adulterated such as Shalaki (Indian Frankincense/Olibanum, *Boswellia serrata*) or Guggulu (Indian Myrrh, *Commiphora wightii,* [46]. Hence, sustainable ingredients from farm are needed such as Drumstick (*Moringa olifera* tree leaves), rich in calcium and highly exported [47]. Glusosamine, a popular health supplement in arthritis is a sea shell product [48]. So it needs a vegetarian option due to the growing trend of veganism globally. Spices can address this as they contain the bio- actives to relive Arthritic pain and inflammation- Vitamin A, C & K, polypohenols, Omega 3 fatty acids, and minerals Calcium, Magnesium, Iron and Zinc [29].

Even in India, about 40% the elderly may be Arthritis affected, it is said in the study by All Indian Institute of Medical Science in metros such as Delhi AIMS [49].

Bioactive ingredient levels are low in the general market samples of spices such as Black pepper (Piperine- 2-4%), Coriander (Quercetin- 0.12%), Turmeric (Curcumin- 2-3%), as the critical agri-inputs to increase the polyphenol content e.g. Potassium for Curcumin by 50% in Turmeric [50, 51]. Higher Potassium inputs also enhances oil content in Coriander [52], for instance. So improving agro-technology can enhance the bioactive potential of the spices.

We demonstrate here the comparative advantage of spices over the standards drug for the treatment of arthritis, to illustrate the alternative approach to drug discovery. Hence, we performed docking study at Rasa Life. Co., (www.rasalsi.com) Pune during 2020 on the key bioactive compounds important spices w.r.t. COX2 (cyclooxygenase) active site (PDB ID 5IKR obtained from PDBsum). **Table 7** shows that the 4 spice ingredients have closeby values and high theraupetic potential are

Spice	Ingredient (conformation)	Site & activity (interactions)- (PDB id 5f19)	Binding energy (kcal/mol)	Remarks
High potential				
Pepper	Piperine (53)	SER530 & ARG 120 (2)	−9.99	Good activity, high probability
Coriander	Apigenin (20) Quercetin	TRP 387 & ASN 382 (2) ALA199, TRP 387 and ASN 382, TRP387, TYR385(A)	−9.94	Stable, high probability
Turmeric	Curcumin (35)	TYR 385- good activity (1)	−8.66	-"-
Less scope				
Ginger	8-shogaol (40)	Amino acid residues- SER530 & MET522 (2)	−7.51	Stable, good activity, high probability
	10- Gingerol (40)	TYR385- Good activity (1)	−7.34	-"-
Fenugreek	Diosgenin (20)	HIS214 (outside site)	−6.80	outside, not feasible
Clove	Eugenol	SER 530 & TYR 385(Chain A)	−6.33	Stable, high probability

Table 7.
Docking study results of Spices active ingredients in COX-2.

viz. Piperine (Black Pepper, −9.99 Kcal/ mol) 'Apigenin' (Coriander, −9.63) and 'Curcumin' (Turmeric, −8.66 with the stability than methotrexate (−8.6), the standard NSAID [53]. The values are also higher than the synthetically designed 'best' molecule- i.e. 4-(4-methyl-1-piperazinyl)-2-phenyl[1]benzofuro[3,2-d] pyrimidine discovered in the Saudi Arabia [53] or isatin (benzohydrazide) [54]. Ginger (−7.51 kcal/mol- 8-Shagaol), and Diosgenin from Fenugreek had the lower than the threshold values (−6.8) so are not considred here here. Other traditional medicine such as Ayurvedic top used herbs such as Behera (*Terminalia bellerica*) & Herra (*T. chebula*) have also shon high anti-inflammatory potential against COX-2 [55].

The earlier tests of herbal ayurvedic medicines in Arthritis treatment yielded encouraging results in Pune city [56], India, and in USA [57]. So this approach needs further exploration. Quercetin from Coriander & Onion, peppers has higher docking score (−12) than even the active ingredients of the commonest herbal drugs Guggul & Shalaki (<10) [58]. Quercetin is also found to be more effective than even aspirin or celecoxib in the inflammation markers cyclooxygenase (COX) that are vital in cancer biology vide studies in Russia [59] and also in India [60]. Hence, the use of these novel molecules in the arthritis context may be found safe, effective and sustainable.

4. Conclusion

Immunity decline is a major cause of the pandemics in the last century and thus inflammation control is a major challenge for healthcare system. Spices and herbs, rich in polyphenols can be vital tool in this regards as they have high antioxidant value and reduce the oxidative damage to the body. Much greater share of vegetarian diet and spices, besides less intensity of packed foods, meat, liquor, Tobacco, refined carbs, soft drinks etc. in India may be driving its higher immunity and lower burden of COVID-19. Pharmacokinetic methods such as molecular docking can be used to design drugs for immunity building and inflammation control. This is shown with the example of Arthritis where Black Pepper, Coriander & Turmeric can provide potent drugs vide docking studies with focus on piperin, quercetin/ apigenin & curcumin.

Author details

Utkarsh Ghate[1*] and Hema Kulkarni[2]

1 Gram Mooligai (Village Herbs) Co. Ltd., Durg, India

2 Government College, Jamgao-R, India

*Address all correspondence to: ughaate@gmail.com

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