**Natural Polyphenol Engineering Field Crops based Diet to Promote Innate Immunity to
Combat Covid-19 Disease**

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Abstract

Due to Covid-19, quarter a million patients have already died worldwide, and evidence showed a clear association between this death and multiple organ dysfunction cytokine storms. No sustainable remedy against this disease has been found and many solutions are being considered to dig out this virus by inventing humoral and cellular immunity capacity building methods as well as food-based remedies. COVID-19 has added an extra burden to the low-income country's health care system while they are still struggling with many challenges including malnutrition, sanitary, safe drinking water. Natural polyphenol engineering field crops (NPEF) based diet could help them to harness innate immunity to prevent or attenuate the SARS-Cov-2 infection as well as reducing the secondary/co-infection by bacteria and fungus of the hospitalized patients. Polyphenols are immunomodulators and have antibacterial, antiviral, anti-cancer, anti-diabetic, anti-inflammatory, coronary heart disease prevention effects together with ability to transport other active molecules. Interaction of polyphenols increase efficacy of vitamin D. This review explored the potentials of polyphenols and their available sources to address the chronic diseases including Covid-19 and proposed a food prescription for Bangladesh to improve their innate immunity system.

Key words: COVID-19, Natural polyphenol engineering field crops (NPEF), Food habit, Immunomodulatory, Innate immunity

1. Introduction

COVID-19 is a global pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the lethal version of previously known coronavirus (CoV). The food supply

chain of these low-income countries mainly depends on field crops including rice, wheat, maize, potato, soybean, tomato, chickpea. Polyphenol rich food, a miracle for human immunity development, should ensure in their daily food list to strengthen their immunity. Natural polyphenol engineering field crop plants (NPEF) endowed rich prospects for them [12]. Polyphenol rich foods from these crops have great potentials as they are easily available to supply to their menu.

2.1 Polyphenol and its importance

.....and other antioxidants have been implicated in protection against host communicable diseases (HCDs) in which oxidative stress is the main contributor including inhibition of adhesion molecule, cytokine and chemokine gene expression, inhibition of platelet function in dengue, augmentation of endothelial nitric oxide release, and other effects on pro-inflammatory factors such as endothelin and matrix metalloproteinase [14]. The direct evidence of acute therapeutic benefits of PC in multiorgan dysfunction remains sparse and searching for novel PC with higher specificity and efficacy may represent a fruitful approach in the development of novel coronavirus therapeutics. The immunomodulatory approach for gaining immune immunity is a considerable priority to inhibit cytokine storm as well as COVID-19 shock management.

Figure 1 explains how polyphenols counteract the endothelial dysfunction to prevent many diseases. *Myrtus* polyphenols can interact with vitamin D which can reduce the death of over 50 percent of the hospitalized patients [95]

2.2 Polyphenol stimulates and boost the immune system

Phytochemicals contribute to boosting the human immune system. The polyphenols such as cyanidin [15], grape polyphenols [16], fisetin [17], xanthohumol [18], quercetin, kaempferol,

daidzein, genistein [19], have the ability to inhibit the secretion of various pro-inflammatory molecules from macrophages or their migration. Orange juice and hesperidin, a flavanone glycoside contained in the juice seem to enhance the functions of macrophages associated with antimicrobial activity [20]. Macrophages are a type of white blood cell of the immune system both nonspecific defense (innate immunity) and specific defense mechanisms (adaptive immunity). Inappropriate or prolonged macrophage activation is largely responsible for various inflammatory states [21].

2.3 Antiviral properties of polyphenols and prospects for the treatment of Covid-19

..... rutin for parainfluenza and influenza virus, apigenin for immunodeficiency and herpes simplex and auzesky virus, naringin and ferulic acid for the respiratory syncytial virus (RSV), luteolin for auzesky virus, morin for potato virus and galangin for herpes simplex virus type [24]. Gerdin and Srenso [25] demonstrated that flavonoid derivatives flavan-3-ol was more effective than flavones and flavonones in selective inhibition of HIV-1, HIV-2, and similar immunodeficiency virus infections. The flavonoid Baicalin, Catechins, demethylated gardenin A, robinetin, chrysin, acacetin, and apigenin with other flavonoids such as robustaflavone and hinokiflavone have also been antiviral effect [26]. Land plants have much successful response by something “novel” to wipes out novel disease including antiviral in human history [27]. RSV virus infect the upper respiratory tract like SARS-Cov-2 to human. These plants and their polyphenols have the potentials to stop SARS-Cov-2 as well as ameliorate Covid-19 disease.

2.4 Polyphenols Biosynthesis and their transporter functionaries in human body

..... Four MATE genes are related to increased antioxidant content and are which are very important for phenolic intercellular transportation processes [43]. It was also proposed that the

translocation of the two other lignin precursors, namely sinapyl and coniferyl alcohol, is ABCG monolignol transporter dependent [44]. The expression pattern of those putative transporters was similar to the transcription factor involved in lignin synthesis and lignin polymerization peroxidase [56]. Interestingly, the dedicated transcriptional network was also determined, underlying the production of benzenoid, as well as phenylpropanoid volatiles, in petunia flowers [45]. Traditionally, MATE have been divided into four superfamilies: the ATP binding cassette (ABC), the major facilitator superfamily, the small multidrug resistance family, and the resistance-nodulation-cell division family [46]. The MATE family of transporters are defined as fifth family [47]. MATE genes are abundant in bacteria and plants the Arabidopsis genome contains at least 56 MATE family members [48], 45 in rice [49], 70 in *Medicago truncatula* [50] and 117 in soybean [51] 67 genes in tomato [44]. Sequencing of the human genome yielded 883 putative transporter genes. Among them 11 is MATE genes [52].

3.0 Natural polyphenol engineering field crops (NPEF) and dietary polyphenols effects

Usually, stressed (biotic or abiotic) plants are rich in polyphenols [27]. In the era of biotechnology, there are many tools to develop the plant's genetic makeup for many phenotypic and phytochemical mitigation called engineered plants [28]. Nature also makes many engineering plants for making variations following natural demands. The plant which deviated from different biotic or abiotic stress showed much variation in respect of polyphenol contents than normal plant [29].

High altitude native people with native food habits are still less affected compared to the western people and the prevalence of chronic diseases is less in that area. The characteristics of high altitude plant-based diets have been found to be potential for global functional food

standardization. These foods are associated with lower risk factors with respect to the development of several chronic diseases [39]. Recently, the Brazilian Congress of Cardiology showed the perspectives of Latin America as a potential producer and consumer of functional food. Approximately 10,000 tons NPEP or their derivatives are exported to many countries, including Japan, the United States, the Netherlands, and Italy. High altitude countries showed better performance against this virus (**Supplemental Table 1**).

4.0 NPEF mixed food prescription for Bangladesh

The low income countries like Bangladesh is rich in cereals, vegetables including dietary fiber, local fruits and some pseudocereals and the food habit comprises accordingly. However, some cereals and pseudocereals have long been underestimated due to modern food habit. The mark increase of the consumption of high-energy density foods (high in fats and sugars) is mentionable with a decrease in physical activity. The rising trends of sedentary lifestyles among urban populations and the social and economic progress led to severe infectious diseases.

Jute is another important crop and its fresh leaves, dried leaves (Nalita) and jute seed are rich in polyphenol [65, 66]. Jute leaves “Saluyot” are used as direct food throughout the world namely ewedu, rama, taushe, kuli-kuli, kwado, ugali, yorubas, mrenda' or 'murere' and as an ingredient in a mucilaginous potherb called "molokhiya". . Acetylsalicylic acid is one of the most widely used drugs as Aspirin may also contain in jute leaves [67]. Jute leaves parts of poorly fermented may works for “Prebiotics” [68] and for transporting dietary antioxidants through the gastrointestinal system [69]. Also, Jute leaves polyphenol, α -amylase and α -glucosidase inhibits type-2 diabetes and Angiotensin converting for hypertension [70]. Bangladesh is not rich in Andean amaranth (*Amaranthus cruentus*) but rich in the other pseudocereal consumed as leafy vegetables

commonly known as “Lalshak” (*Amaranthus gangeticus*, *Amaranthus tricolor*) and “datashak” (*Amaranthus dubius*). Jute leaves may rebirth as vegetable against COVID-19 or other infectious disease for its many functionad food versions.

. The dietary sources of major polyphenol, anthocyanins and flavonoid from Rice, Jute, Maize and Potato are showed in the table-2.

5.0 Conclusion and perspectives

Diet high in polyphenols can stimulate the immunity system to increase the innate immune cells such as neutrophils [76], natural Killer Cells (NK) [77], Vagal Nerve modulation [78], and metabolic Control of immunity [79] in the human body and in the long run adaptive immune cells to gain strong immunity [80], which help can reduce the viral e.g. SARS-Cov-2, infection at the beginning and attenuate or even stop cytokine storm of the severely infected patients. Ensuring the suggested NPEP based polyphenols in diet could help the people of low-income countries like Bangladesh to reduce the burden of Covid-19.

supports the "Darwinian medicine" notion [81]. Bangladeshi food habit is based on cereal from vast. So the NPEP from cereal is a well-suited future food prescription [85].

The effects of polyphenols to combat many viral and chronic diseases are confirmed based on the previous research findings and may work to fight against Covid-19 and new experiments are necessary to get direct experimental evidence or clinical trials specific to SARS-Cov-2. These polyphenols are imperative to improve innate immunity to defend primary infection as well as to save hospitalized patients from secondary infection by bacteria or other pathogens. We also suggest further molecular and clinical trials using these polyphenols to find low cost and easily available food-based antiviral drugs or therapies.

6.0 Conflict of interests

Authors contributed equally and declare no conflicts of interests of this article.

7. Acknowledgements

Authors like to thanks Dr. Zaid Ahmed, Assistant Professor and Dr. Mainul Hossain, Associate Professor in the Department of Biochemistry and Microbiology under the School of Health and Life Sciences at North South University, Dhaka, Bangladesh, for their valuable comments and suggestions.

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Table 1. List of important polyphenols in NPEP field crops such as Rice, Jute, Maize and Potato crops

Polyphenol type	Active Compound(s)	Effective against/for	Sources in NPEF*	Ref.
Anthocyanin	Cyanidin-3-O-galactoside	Anti-cancer, Anti-inflammatory	BR	95
	Cyanidin-3-O-rutinoside	Anti-oxidant, anti-cancer etc.	BR	95
	Cynidin-3-glucoside	Anti-inflammatory, anti-diabetic	PM, PP, J	96, 91
	Pelargonidin-3-glucoside	Anti-inflammatory, Anti-oxidant	PM	96
	Peonidin-3-glucoside	Chemo-preventive, disease prevention	PM	96
	Pelargonidin glycosides—3-O-p-coumaroylrutinoside-5-O-glucoside	Anti-bacterial, Anti-oxidant	RP	97
	Malvidin glycoside 3-O-p-coumaroylrutinoside-5-O-glucoside	Anti-oxidant protection	PP	97
	Petunidin—3-O-p-coumaroylrutinoside-5-O-glucoside	Inhibition of pro-inflammation signal	PP	97
	Peonidin-3-rutinoside-5-glucoside	Anti-cancer, prevent cardiac disease	PSP	98
Phenolic Acid	p-hydroxyphenyl	Anti-microbial, anti-inflammatory	PM	92
	1,3-di-O-caffeoyquinic, 3,4-di-O-caffeoyquinic,4,5-di-O-caffeoyquinic, 4-O-caffeoylquinic, Apegenin-7-0-glucoside, Protocatechuic	Anti-microbial, anti-inflammatory	J	90
		Anti-cancer, anti-inflammatory	J, PM	90, 97
	p-coumaric, Cryptochlorogenic, Gallic, Neochlorogenic, p-hydroxy benzoic, p-hydroxyphenyl acetic	Anti-virus (enterovirus 71, HSV, HCV), Anti-human deficiency etc.	BR, RP, PM,J	95, 97, 102
	Quinic	Astringent, Anti-oxidant	J, YM	90, 99
	Rosmarinic acid	Anti-microbial, anti-inflammatory	J, BR	90, 9
	Caffeic	Anti-cancer, anti-inflammatory	J, PM, RP	90, 97
	Chlorogenic	Anti-oxidant, anti-inflammatory	RP,PM, J	97, 92, 90
	cis- sinapic	Anti-microbial, anti-inflammatory	BrR, RP	95, 97
	cis-ferulic acid	Anti-viral (RSV), anti-inflammatory	PP, J, PM, CR	95,97, 92, 90
Flavonoid	Apigenin	Anti-inflammatory, anti-depressive	CR, J	90,95
	Catechin	Immuno-stimulator, antioxidant etc.	CR, PM, P	95, 96, 97
	Epicatechin, Myricetin, Tangeritin, Taxifolin	Anti-microbial, anti-inflammatory	BrR, BR	95
	Isorhamnetin	Anticancer, anti-diabetic	BR, RR	95,100
	Kaempferol	Anti-angiogenesis, Anti-inflammatory	BR, RR, RP, PM, J	90, 92, 95, 97
	Morin	Anti-bacterial, neuroprotective etc.	CM	92
	Naringenin	Anti-viral (HCV), Anti-inflammatory	B/RR, PM, J	90, 92, 95
	Cirsilineol, Cirsiliol, Naringin, α -glucosidase, Quercetrin (quercetin-3-O rhamonoside)	Anti-diabetic, Anti-oxidant, immune-stimulator	J	90
	Rutin	Para influenza, Influenza virus, Murin norovirus, Inhibit HB virus gene exp.	BR, PM, RP	90, 92, 95
	Tricin	Anti-bacterial, anti-inflammatory	BR, RR, BrR	95
	Quercetin-3-o-glu-rut	Anti-viral (Myaro virus)	RP	93
	Quercetin	Anti-viral (Rabies, influenza, polio, RSV etc.), anti-cancer etc.	BR, PM, J	90,95, 92

	Luteolin	Anti-inflammation, Anti-oxidant	B/RR, J, M	90,95, 101
	Hesperitin	Immune health support etc.	RG, PM	92,95
	Chrysoeriol aglycones	Anti-bacterial, anti-diabetic etc.	R	95,101
	Eriodictyol	Anti-cancer, Anti-inflammation		
	Isoorientin	Anti-viral, Anti-bacterial, fungal		
	Maysin	Anti-biotic, Anti-oxidant		

*BR, Black rice; BrR, Brown rice, RR, Red rice, PM, Purple maize; YM, Yellow maize; PSP, Purple sweet potato; PP, Purple potato; CM, Colored maize, RG, Rice grain; RP, Red potato; R, Rice, J, Jute; M, Maize;

Supp. Table 1: Worldometer COVID-19 update in the world high altitude regions as of May 5th, 2020

Regions	Death by COVID-19	COVID-19 cases	Height above the sea level
Tibet	0	1	4000
Bhutan	0	7	2500
Nepal	0	82	3000
Kyrgyztan	11	843	2750
Ethiopia	3	124	3000
Peru	782	28699	2500
Venezuela	10	325	1500
Colombia	253	5597	2000
Bolivia (La paz)	50(0)	950(1)	4000
Ecuador (Quito)	665	23240	2850
Chile	198	13813	2400
Colorado, USA	680	13441	2000

Figure 1. Mechanisms of polyphenols to counteract of endothelial dysfunction including prevention of low density lipoprotein (LDL) oxidation and atheromatous plaque deposition; suppression of nuclear factor kB (NFkB), cyclooxygenase (COX), lipoxigenase (LOX) and thromboxane A2 (TXA2); inhibition of platelet aggregation and thrombus formation; decrease of endothelin-mediated vasoconstriction; release of nitric oxide and vasodilation. Adpted from Iriti, Marcello & Faoro, Franco. (2008)

Figure 2. Phenylpropanoid pathway leading to flavonoids and non-flavonoid polyphenols proanthocyanidins. Phenylalanine derivative is condensed with 3 molecules of malonyl-coenzyme A (CoA) by chalcone synthase (CHS) to form chalcone, then converted to naringenin, the precursor of flavonoids, by chalcone isomerase (CHI). Then proanthocyanidins biosynthesis. Nonflavonoid polyphenols biosynthesis also from phenylpropanoids by the enzyme stilbene synthase (STS). Adapted from Iriti, Marcello & Faoro, Franco. (2008).