Review Article

Potential of the Triad of Fatty Acids, Polyphenols, and Prebiotics from Cucurbita against COVID-19 in Diabetic Patients: A Review

Abstract

Though the scientific community of the entire world has been struggling to create preventive and therapeutic drugs for coronavirus disease 2019 (COVID-19), the role of nutraceuticals has been hitherto neglected. Established role of fatty acids and polyphenols in combating lifestyle disease can be harnessed to play a significant role in the prevention of this disease. The synergistic effect of these phytonutrients and prebiotics is anticipated to prove beneficial for prevention as well as attenuation of COVID-19 infection. Presence of fatty acids, polyphenols and prebiotics in vegetables from the Cucurbitaceae family makes them an attractive choice for being used as a nutritional supplement during COVID-19. These are known to attenuate the excessive immune response which may prove to be beneficial in preventing and mitigating COVID-19. Use of prebiotics to promote the growth of probiotics has also been recommended for the prevention and cure of COVID-19. However, no such report exists in literature that throws light on such role of cucurbita plants. The present review focuses on the role of the triad of fatty acids, prebiotics and polyphenols present in cucurbita plants in controlling systemic inflammation and endothelial damage, the two main etiopathological factors involved in COVID-19. Cucurbita plants are rich in all these components and their inclusion in diet would be an effective strategy to combat COVID-19. The main focus of the review is to discuss the role of various components of the plants of Cucurbita family, taken as dietary component, in prevention and control of the ongoing pandemic COVID19.

Keywords: *Diabetes mellitus, fatty acids, microbiome, polyphenols, prebiotics, SARS-CoV-2*

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Introduction

Diabetes mellitus

Diabetes mellitus (DM) which is a group of metabolic disease has acquired epidemic proportions in the twenty-first[t] century. More than 460 million people in 2019 are reported to be suffering from some form of DM and the number is anticipated to reach approximately 580 million by the end of this decade.[1] Diabetic patients are susceptible to a number of co-morbidities, generally resulting in reduced quality of life. It also predisposes patients to a number of opportunistic infections.[2]

DM is a chronic metabolic disorder of endocrine origin arising because of the failure of the body to respond to the elevated blood glucose levels. This abnormality in carbohydrate metabolism is attributed either to deficiency of insulin secretion or to dysfunction of pancreatic β cells responsible for producing, storing and releasing insulin. Failure of the body to utilize insulin because of insulin resistance can be another etiopathological factor.[3,4] However, apart from insulin deficiency or lack of utilization, there are many other causes of DM including various pathophysiological changes.[5] In fact, the causes of diabetes popularly known as "Dirty Dozen" include pancreatic β-cell failure, insulin resistance, hepatic gluconeogenesis, deranged adipocyte metabolism, hyperglucagonemia, incretin defect, increased renal glucose reabsorption, neurotransmitter dysfunction, central appetite dysregulation, gut microbiota, deregulation of the immune system and abnormal activity of hormones, namely dopamine, testosterone, vitamin D, and renin-angiotensin system.[6]

Diabetes can be categorized into are four types as classified by The American Diabetic Association. These include two forms of idiopathic diabetes, that is, type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes. Third category is that of gestational diabetes which develops during pregnancy while the fourth one, that is, secondary diabetes is associated with other specific conditions.[7,8] Fourth type, that is, pre-diabetes is a state in

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which blood glucose levels are high but enough to be diagnosed as type 2. It can be prevented for developing into type 2 diabetes by weight loss, life style changes, and medicine.[9]

Advent of DM leads to certain microvascular and macrovascular complications including diabetic neuropathy, diabetic retinopathy, cardiac myopathy, and diabetic foot ulcers.[10,11] Coprevalence of these diseases is related to extent of hyperglycemia, its management and age.

Immune system in the human body is the complex host defense system that protects it against diseases. Its main function is to protect the body from any outside invaders such as viruses, bacteria, fungi and toxins as well as from intrinsic ones like tumors.[12] The primary components of the immune system include thymus, spleen, component system, bone marrow, and lymph nodes.[13] Immune malfunction is observed in cases of diabetic patients who are generally more prone to infection.[14] Due to the compromise in the immune function, the whole physiological system is not able to respond appropriately to a physiological insult.[15]

SARS-CoV-2 and diabetes

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly virulent and fatal human pathogen that emerged in Wuhan, China in 2019 and has led to a global pandemic.[16-18] Diabetic patients have been reported to be more prone to SARS-CoV-2 with higher rate of mortality and co-morbidity.[19,20] Mortality in people with diabetes has been reported to be 7.3% vis-à-vis 2.3% overall by Chinese Centre for Disease Control and Prevention in a report on 72,314 cases of Coronavirus disease 2019 (COVID-19).[21] Though a relationship between diabetes and infection has been clinically well established,[22] diabetes has definitely emerged as a risk factor which contributes to the severity and mortality of COVID-19.[23]

Diabetes and cardiovascular diseases are considered amongst the highest risk factors associated with SARS-CoV-2 fatality according to a study that included more than 17 million UK adults.[20]

Microbiome

A number of studies have reported that commensal gut microbiota forms a complex ecosystem that is vital for the maintenance of human health.[24-26]

Interestingly, the cells of human gut microbiome outnumber the total number of cells in the human body and have an essential influence on human health stimulating the immune system, managing gastrointestinal infections and protecting neuronal damage.[27,28] In certain pathogenic conditions, microbial imbalance of gut microbiome which is known as dysbiosis occurs that leads to a number of diseases such as diabetes, neuropsychiatric conditions, auto-immune diseases, tumors as well as allergic disorders.[29] Moreover, this microbiome imbalance leads to the transmission of pathogen-related molecular that may lead to an abnormal immune response to the host.[28] Villanueva-Millán *et al.* reported that the majority of gut bacteria in healthy persons belong to four phyla, that is, *Actinobacteria*, *Bacteroidetes, Firmicutes* and *Proteobacteria.*[30] Interestingly, these four phyla are also present in the lung.[31,32] Existence of "gut-lung axis" has also been reported which demonstrates that there is communication between the microbiome in the lung and that in the gut. Dysbiosis or inflammation in the gut, therefore, may lead to pulmonary morbidities and *vice versa*.[33,34] Gastrointestinal symptoms have been extensively reported amongst SARS-CoV-2 patients indicating gut inflammation.[35] The SARS-CoV-2, an enveloped virus, enters host cells by engaging with the angiotensin-converting enzyme 2 (ACE2) as the entry receptor which can be blocked by the cellular serine protease TMPRSS2 inhibitor.[36] ACE2 receptors are found in both respiratory and gastrointestinal tract.[37] Consequently, SARS-CoV-2 is found in the gastrointestinal tract as this virus can bind to ACE2 receptors. In a study reported in fifteen SARS-CoV-2 patients, Zuo *et al.* found the possible relationship between the presence of some gut microbiota and SARS-CoV-2. The study showed a negative correlation between *Bacteroidetes* species which suppress the ACE2 expression and SARS-CoV-2 severity. Other common species *Bacteroides dorei, B. thetaiotaomicron, B. massiliensis,* and *B. ovatus,* on the other hand, showed negative correlation with fecal viral load of SARS-CoV-2.[37]

Pro-inflammatory T helper 17 cells (Th17 cells) have a potential pathogenic role in many metabolic syndromes including type 2 DM secreted cytokines Interleukin 17 (IL-17A), IL-17F and IL-22 that are known to reduce insulin signaling, leading to insulin resistance and development of type 2 DM.[38,39] Many of these biochemical changes are also associated with gut dysbiosis.[39]

Materials and Methods

Available electronic databases such as Web of Science, ScienceDirect, PubMed, Scopus and Google Scholar were used to search for the *in vitro* as well as *in vivo* effects of fatty acids, polyphenols and prebiotics from the plants of Cucurbitaceae family. Keywords used for literature search were "Cucurbitaceae", "Cucurbita", "fatty acids", "polyphenols", "prebiotics", "fibers", individual plants of Cucubitaceae family and their combination. The articles were screened for relevance by going through their abstract. All the articles pertaining to physicochemical, physiological, neuroprotective effect of lycopene have been included in the manuscript.

Fatty Acids in Cucurbita and Their Role

Fatty acids, which are the building blocks of the fat in the bodies of humans and animals, are molecules with long straight chains of carbon atoms with a carboxyl group at the its end.[40] Being an essential component of cell membranes, they generally exist in the form of phospholipids and glycolipids. They play vital structural, functional and physiological roles in the body, they are classified into two types, that is, essential and non-essential. The essential fatty acids are polyunsaturated fatty acids (PUFA), which cannot be synthesized in the human body and need to be taken through diet source.[40,41] Saturated fatty acids and unsaturated fatty acids are described below.

Saturated fatty acids

These are vital for a number of biological functions of the human body. SFAs are synthesized by the human body and are also obtained from dietary sources like vegetable oils or animal fats.[41] SFAs act as energy suppliers and storage material, building blocks of certain hormones and cell membranes. They also contribute towards mechanical functions like shock absorption and thermal insulation.[42-44] Moreover, SFAs are involved in some signaling pathways involved in maintenance of homeostasis.[45,46] During their metabolism, SFAs are converted to triacylglycerols by esterification. This takes place in the intestinal mucosa cells. After that, they become a part of chylomicrons, bind to albumin in the circulatory system and enter the cells through Fatty Acid Transport Protein.[47,48] Palmitic acid, myristic acid and lauric acid, which are C16:0, C14:0 and C12:0, respectively, are important in such signaling pathways.

SFAs are essential for the normal functioning of white blood cells. They are also required for the maintenance of stability of proteins.[49] Certain SFAs like lauric acid possess antimicrobial properties also.[50]

Short chain saturated fatty acids (SCFAs) are aliphatic fatty acids of chain length ranging from 1–6 carbons. These include acetate, propionate, butyrate, iso-butyrate, valerate, iso-valerate and hexanoate and are generally produced by anaerobic microflora of the gut from indigestible dietary fibers. SCFAs are reported to provide energy and act as substrates for synthesis of sugars as well as lipids. They are also used by cytokines to modulate certain metabolic activities.[51] They are widely reported to reduce the serum levels of glucose, insulin resistance as well as inflammation, and enhance the protective Glucagon-like peptide-1 secretion.[52]

Various characteristics of these fatty acids, have been described in Table 1.

Monounsaturated fatty acids (MUFAs)

These fatty acids contain only a single point of unsaturation, in the form of a double bond connecting two carbon atoms. MUFAs are reported to reduce the risk of heart disease by decreasing the low-density lipoproteins (LDL).[72] They are also involved in supply of vitamin E to the body as vitamin E levels in plasma have been reported to be increased with inclusion of MUFAs in diet.[73] They are reported to play a significant role in the absorption and metabolism of fat-soluble vitamins, that is, vitamin A, D, E and K.[74,75] Further details can be found in Table 1.

MUFAs are known to increase the levels of the high-density lipoproteins (HDL) while lowering the levels of LDL. By this dual effect, they exert vasculoprotective as well as cardioprotective effects. MUFAs are needed during the development of nervous system in children and are also involved in improving the brain function in adults.[76] Oleic acid, a MUFA of long chain length, has been widely reported as a healthy fat.[77,78]

Polyunsaturated fatty acids (PUFAs)

These fatty acids have two or more carbon-carbon double bonds in their chain and are the common constituents of lipid membranes. These are reported to play a significant role in both the development as well as functioning of the nervous system. Similar to MUFAs, they are also reported to decrease LDL levels while increasing the of HDL plasma levels thereby preserving the health of the cardiovascular system.[72]

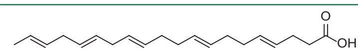
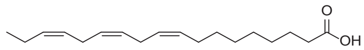
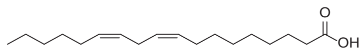
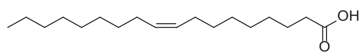
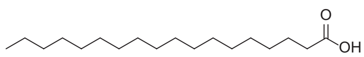
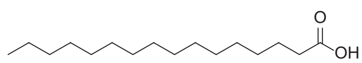
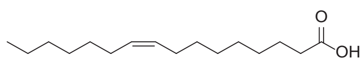
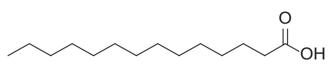
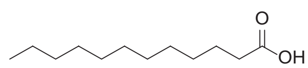
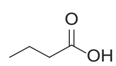
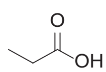
PUFAs include linoleic and linolenic acids, which are described as ‘essential’ because of the fact that the human body is not able to synthesize these two fatty acids [see Table 1]. They are vital components of cell membranes and are involved in regulation of blood pressure as well as inflammation.[79] Both linoleic acid and linolenic acid along with arachidonic acid act as ligands for peroxisome proliferator-activated receptors, that is, PPARγ and PPARα. They are thus, involved in modulation of PPAR γ dependent regulation of anti-inflammatory and anti-diabetic effects.[60,61] They also contribute towards modulation of angiogenesis, apoptosis and immune response.[80]

Role of cucurbita fatty acids

One of the most dangerous risk factors which can lead to the morbidity and mortality of SARS-CoV-2 in the patients is the Heart Fatty acids binding protein (HFABP).[81] Linolenic acid has been reported to inhibit adipocyte differentiation which may lead to a decrease in the expression of HFABP.[82,83] Zhang and Liu (2020) reported that linoleic acid, by RNA export machinery, could decrease influenza virus replication. However, clinical studies are required to extrapolate these findings to SARS-CoV-2.[84] It has been claimed that PUFAs have an essential role to stop the virus from invading the cell.[85] However, this claim is based on animal studies and its application to human cells needs scientific validation.

Consuming high-fat and high-sugar diet impacts the gut microbiome and might lead to circadian rhythm disruption.[86] Backhed *et al.* were the first to demonstrate the gut microbiome in metabolic regulation in mice. Mice lacking a gut microbiome were characterized by a lower fat mass whereas transplanted gut microbiome mice resulted in higher production of leptin and in increased fat mass.[87] Stimulating the gut microbiome to produce SCFA is an essential role, to manage metabolic disorder as SCFA improve insulin response after oral glucose-tolerance test.[88] Recently Coutzac *et al.* discovered that SCFAs that are produced by gut microbiota are able to produce an antitumour effect in patients. This study shows the benefit of using fatty acids as immunomodulators.[89] Moreover, with respect to SARS-CoV-2 as an enveloped virus, fatty acids chain side such as in ginkgolic acids could be used to treat SARS-CoV-2.[90]

Table 1: Properties and functions of various fatty acids

Fatty acid (Carbon:unsaturation)	Chemical structure	Functions	Reference
Eicosapentaenoic acid (20:5)		Immunomodulator	[53]
Linolenic acid (18:3) ω−3/6		Immunomodulator, glycaemic control, cardioprotective, anti-inflammatory, ↓ risk of AD	[54-57]
Linoleic acid (18:2) ω−6		Regulates blood pressure, blood clotting, blood lipid level, ↓ the risk of CHD	[58,59]
Oleic acid (18:1) ω−9		Fatty acid storage, long-term source of energy, layer of insulation, antihyperglycemic, ↓ metabolic LDL, HDL	[60,61]
Stearic acid (18:0)		Hypocholesterolemic, might prevent Parkinson's disease	[62,63]
Palmitic acid (16:0)		Antioxidant, special structural and functional roles in utero and in infancy, glycemic control	[64]
Palmitoleic acid (16:1)		Antihyperglycemic, anti-inflammatory	[65]
Myristic acid (14:0)		Possible treatment of immunodeficiency diseases, ↓ risk of diabetes	[66]
Lauric acid (12:0)		Antimicrobial activity, anti-inflammatory, antitumor	[67,68]
Butyric acid (4:0)		Anti-inflammatory, influences brain function, improve energy metabolism	[69]
Propionic acid (3:0)		Promotion of satiety and reduction in cholesterol, anti-inflammatory, antihyperglycemic	[70,71]

AD: Alzheimer's disease; CHD: Coronary heart disease; LDL: Low-density lipoprotein; HDL: high-density lipoprotein

It is possible to use nutritional sources to help patients with DM to either prevent, or treat, infection with SARS-CoV-2, and reduce both morbidity and mortality in such CoV-2 patients with co-morbidities.[91,92] Potential source of these components are the plants belonging to the *Cucurbita* genus. This consists of squashes/gourds such as pumpkin (*C. pepo*) and butternut (*C. moschata*). The superior health promoting effects of phytonutrients in the form of plant products as compared to those in their *per se* form accrue from a complex interplay of cell signaling, biochemistry and physiology. Utilizing the concept of food synergy to increase the bioavailability of a phytonutrients is widely reported in literature.[93] Presence of beneficial fatty acids along with fiber content is expected to have an effect on glycemic index.[94]

Butternut squash seed oil contains three types of fatty acids, that is, SFAs, MUFAs and PUFAs. Among the SFAs, palmitic acid constitutes 25% of total fat content (TFC) while stearic acid constitutes 3% TFC. As far as MUFAs are concerned, oleic acid constitutes about 10% of TFC. Among PUFAs, linoleic acid constitutes 23% TFC while linolenic acid makes up 36% TFC.[95]

Pumpkin seed oil is reported to have a high content of both essential and non-essential fatty acids. While the SFAs include lauric acid, myristic acid, palmitic acid and stearic acid, MUFAs are majorly constituted by palmitoleic acid and oleic acid as MUFAs and linoleic acid and linolenic acid are the major PUFAs.[96]

The presence of high amounts of oleic and linoleic acids help in significant reduction of the plasma cholesterol levels on regular consumption. It is known to decrease the plasma levels of LDL and increase those of HDL.[58] The oil obtained from the pumpkin seeds has been reported to have certain therapeutic activities such as antifungal, antidiabetic, and anti-inflammatory activities.[97] Anti-inflammatory activity of oil obtained from *C. pepo* has also been reported in its wound healing effect. In a study on rats, the skin appendages and well-organized collagen fibers without inflammatory cells were found to reappear with the use of *C. pepo* extract.[98] Cucurbita has been used as traditional medication in most regions of the world.[99] Despite the fact that the seeds of butternut squash and pumpkin have shown promising therapeutic potential, only a few detailed reports are available on their composition and the properties of their oil for achieving euglycemia. The oil extracted from pumpkin was reported to exhibit hypoglycemic effects in alloxan-induced diabetic rats.[100] A number of studies indicate that the compounds found in pumpkins are useful in the management of insulin levels in the plasma.[101,102]

Ezuruike and Prieto (2014) reported Linoleic acid, Oleic acid, Linolenic acid, Myristic acid, and Palmitoleic acid, in the plant of Cucurbita, as relevant components.[103] Interestingly, a recent study by Xiao *et al.* discovered the present of SARS-CoV-2 in the faeces of infected patient.[104] Li *et al.* reported that microbiome in the body have a suppressive role for invading virus through different mechanisms.[105] However, Ghaffari, *et al.* reported that fatty acids such as oleoylethanolamide inhibit the pathway of SARS-CoV-2 infection.[106] Recently, the KD Pharma Group and its partner SLA Pharma announced that the new drug candidate which is a long-chain omega-3 marine fatty acids derived from eicosapentaenoic acid will soon enter clinical trials as a potential treatment for the treatment of patients with symptoms of SARS-CoV-2.[107] For non-severe patients, fatty acids could be included in their diets as a nutritional component.[108] Hence, including Cucurbita FAs in the diet of diabetic people is recommended.[109]

Cucurbita flowers have been reported to have the ability to stimulate humoral immune response *in vivo*.[110] It has also been stated that pumpkin seeds have immunomodulatory effects which can be used as an immunonutrient and anti-atherogenic hypolipidemic.[111,112] However, these studies were performed in animal models and the whole pumpkin powder seed was used. Therefore, more clinical studies need to be carried out.

Polyphenols in Cucurbita and Their Role

Polyphenols, the largest class of phyto-bioactives, are generally produced as secondary metabolites in plants. They are reported to exert protective action against ultraviolet radiations, pathogen infection, and oxidative stress.[113] They generally contain one or more phenolic ring and can be classified into flavonoids (anthoxanthins, flavanones, flavanonols, flavans, antocyanidins, isoflavonoids and neoflavonoids), phenolic acids (caffeic, carnosic, ferulic, gallic, *p*-coumaric, rosmarinic, vanillic), polyphenolic amides (capsaicinoids, avenanthramides) and other polyphenolic compounds like stilbenes and lignan [see Table 2].[114-116]

In addition to their widely reported antioxidant and anti-inflammatory activities, a number of reports are available on the antiviral potential of polyphenols against several pathogens such as Epstein-Barr virus,[117,118] enterovirus,[119] herpes simplex virus,[120] influenza virus[121] and other virus causing respiratory tract-related infections.[122] The antiviral action of polyphenols

Table 2: Quantitative analysis of polyphenols present in some of the plants belonging to Cucurbitaceae family

Polyphenol	Polyphenol content (mg/100g) Benincasa hispida	Lagenaria siceraria	Momordica charantia	Trichosanthes anguina	Cucurbita maxima	Reference
Gallic acid	52.5	9.2	338.6	2.15	2.58	[134-138]
Protocatechuic acid	126	3.2	3.59	10.18	5.09	[135,138-141]
4-Hydroxybenzoic acid	-	7174	0.18	1.473	10.04	[138,139,141-143]
Vanilic acid	-	6337	2.15	0.740	8.81	[135,138,141,142,144]
Chlorogenic acid	-	364	10.73	-	6.85	[135,138,142]
Caffeic acid	79	3	0.42	0.953	17.75	[138-141,143]
p-coumaric acid	-	3120	0.47	0.541	0.03	[135,138,139,141,142]
Ferulic acid	0.66	7670	0.18	0.66	13.60	[136,138,139,143,145]
Syringic acid	-	-	2.10	1.460	2.04	[135,139,141]
Sinapic acid	-	-	-	3.758	32.0	[138,141]
Rutin	1.28	-	2.9	1.95	51.92	[136,138,146]
Kaempferol	-	-	0.27	0.35	0.046	[136,139]
Isoquercetin	-	-	-	-	5.54	[138]
Astragalin	-	-	-	-	28.03	[138]
Myricetin	-	-	-	-	9.04	[138]
Quercetin	0.4	6.1	8.0	0.46	6.97	[136,137,139]
Fatty acids						
Linolenic acid	-	9.0	5870	-	2.24	[147-149]
Linoleic acid	-	61.4	6310	-	49.41	[147-149]
Oleic acid	-	4.0	3920	-	25.41	[147-149]
Stearic acid	-	660	-	-	4.51	[147-149]
Palmitic acid	-	2.0	7360	-	20.78	[147-149]
Palmitoleic acid	-	100	210	-	-	[147-149]
Myristic acid	-	100	90	-	0.009	[147-149]
Lauric acid	-	-	250	-	1.336	[149]

is attributed to inhibition of viral replication, protein synthesis, gene expression, and nucleic acid synthesis.[117]

Till date, the world is struggling to treat Covid-19 infection which enforces the physicians to use widely known antivirals and corticosteroids. In addition to them, herbal extracts of a number of Chinese medicinal plants such as *Cibotium barometz, Gentiana scabra, Dioscorea batatas, Cassia tora and Taxillus chinensis* were found to inhibit SARS-CoV replication.[123] Only a few reports are available on the *in vitro* studies of the effect of polyphenols (forsythoside A, (-)-catechin gallate, (-)-gallocatechin gallate, resveratrol as well as polyphenols from *Broussonetia papyrifera* and *Sambucus nigra*) against coronavirus.[124-128]

Pumpkin is rich source of carotenoids (lutein, most abundant), phenolic acids, flavonols, saponins, mineral components and vitamin C.[129-131] The various phenolic acids found in pumpkin varieties are gallic acid, protocatechuic acid, 4-hydroxybenzoic acid, 4-hydroxybenzaldehyde, vanilic acid, chlorogenic acid, caffeic acid, *p*-coumaric acid, ferulic acid, syringic acid and sinapic acid.[132] The content of flavonols in pumpkin was reported to be less than phenolic acids. Among the various flavonols, rutin and kaempferol are the most abundant flavonols found in all the pumpkin varieties. The others flavonols are isoquercetin, astragalin, myricetin and quercetin.[133] The chemical structures of these phenolic acids and flavonols present in pumpkin are depicted in [Figure 1].

In another study, the antioxidant and radical scavenging effect of *Cucurbita* fruits (18 cultivars of the species *C. maxima* Duch., *C. moschata* Duch., *C. pepo* L., and *C. ficifolia* Bouché) were assessed. All the species were found to show remarkable antioxidant and radical scavenging properties mainly attributed to the presence of polyphenols. It is pertinent to note here that both these properties are of immense use in combating the COVID19 infection.[113,139]

Polyphenolic compounds have been reported to exhibit potency against Covid virus in a number of studies, and can be considered as potential nutraceutical(s) for the treatment of SARS-CoV-2 infection. Polyphenols have been reported to block the production of cytokines by senescent cells (senescence-associated secretory phenotype) and adipocytes, as well as modify the ACE-1/ACE-2 ratio, which can potentially result in beneficial effects in COVID-19[150] [Figure 2]. Rutin, one of the major flavonols present in pumpkin varieties, has been reported to exhibit good binding characteristics with SARS-CoV-2 main protease and host toll-like receptors in *in silico* studies, indicating it as a novel therapeutic option, having its impact *via* virus-based and host-based anti-CoV strategies.[151-153] Similarly, the other flavonoids found in pumpkin, that is, kaempferol and quercetin were reported to SARS-CoV-2 main protease in molecular docking studies, and therefore may act as anti-COVID-19 agents.[154,155] However, further research is necessary to investigate their potential medicinal use.

Prebiotics in Cucurbita and Their Role

Prebiotics are the indigestible plant fibers that act as growth substrates specific for beneficial microorganisms. They are widely reported to reduce gut inflammation, obesity, and lipid accumulation. These not only improve gut health but also lead to inhibition of pathogens and stimulation of immune system owing to their ability to modulate the type, numbers, composition and even activity of human microbiota.[156] Administration of prebiotics is known to reduce the inflammation and infection in lungs as well as other respiratory ailments such as asthma and chronic obstructive pulmonary disease.[157] This interplay is facilitated by the gut lung axis. Prebiotics include fructans, oligosaccharides, arabinooligosaccharides, isomaltooligosaccharides, xylooligosaccharides, resistant starch, lactosucrose, lactobionic acid, galactomannan, polyphenols and polyunsaturated fatty acids. An inverse correlation has been established between prebiotic consumption and serum levels of inflammatory cytokines including C-reactive protein, interleukin (IL)-6, IL-18 and tumor necrosis factor-alpha (TNFα).[158] The event of acute rise in these very cytokines called as cytokine storm has been reported to play a crucial role in severity of the disease and mortality therefrom.[159] SCFAs like acetate, propionate and butyrate are the main components of immunomodulatory signals which are produced by gut microbiome.[160] A daily intake of just 6 g of prebiotics has been reported to increase the levels of SCFAs substantially.[161] No information, however, is currently available on the direct effect of prebiotics on the COVID-19 infections, although an indirect relationship may be drawn. Further, a number of clinical trials have proven the efficacy of prebiotics in diabetes management by improving the barrier function and translocation of bacterial lipopolysaccharide.[162]

As mentioned previously, prebiotics are considered as dietary fiber which stimulate health promoting microorganisms.[163] Role of prebiotics in handling the COVID-19 infection has been attributed to the involvement of gut lung microbiota axis.[158] A number of studies have reported the effect of prebiotic component of various Cucurbita plants.[164] Prebiotic effect of *C. maxima* was demonstrated by Lokuge *et al.* in pigs showing an increase in beneficial microorganisms and a decrease in coliform bacteria.[163] Pectin extracted from *C. maxima* was found to exhibit strong bifidogenic effect. An anti-hypertensive effect of a combination of pectin from *C. maxima* along with whey protein hydrlysate was also observed.[165] In fact, the prebiotic potential of oligosaccharides obtained from *C. moschata* pulp were shown to be better than even inulin (considered as golden standard prebiotic) in terms of their reistance to hydrolysis by gastric juice and equivalent in terms of stimulation of the growth of Lactobacilli.[166] Even waste derived from pumpkin peel and pulp (30:70 w/w) were found to to exhibit excellent prebiotic properties for the growth of *Lactobacillus casei*.[167]

A novel protein-bound polysaccharide obtained from the seeds of *C. maxima* exhibited α-amylase and α-glucosidase inhibitory activity and thus can be used as an antidiabetic agent.[168] In another study, seed flour from *C. maxima* was reported to

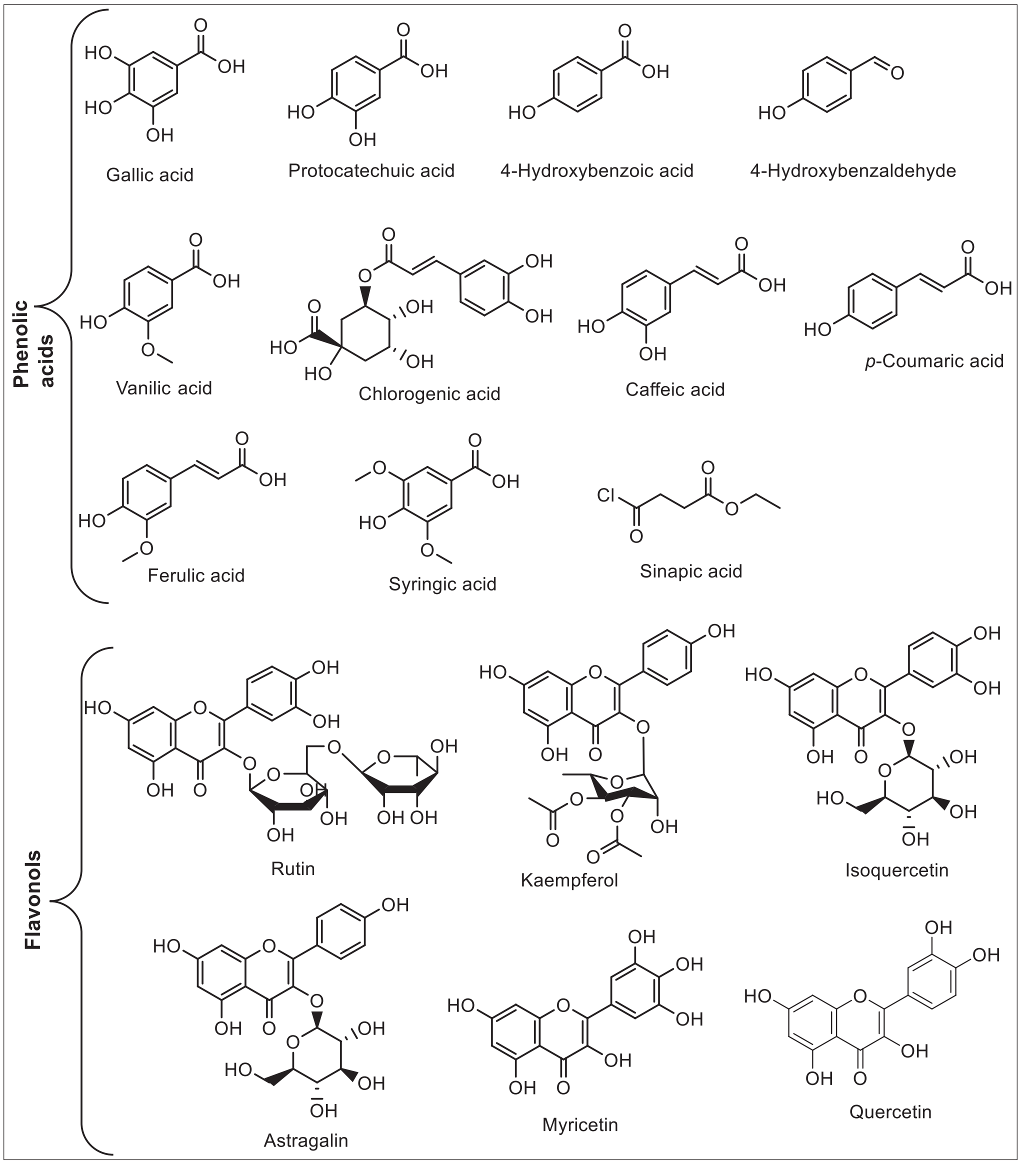


Figure 1: Chemical structures of phenolic acids and flavonols present in pumpkin

interfere in the rat metabolism decreasing significantly the serum glucose and triacilglycerides levels.[169]

Production of SCFAs is one of the key roles played by prebiotics in association with the colonic bacteria. No information, however, is currently available on the direct effect of prebiotics on the COVID-19 infections, although an indirect relationship may be drawn. Further, a number of clinical trials have proven the efficacy of prebiotics in diabetes management by improving the barrier function and translocation of bacterial lipopolysaccharide.[170] The SCF producing ability of five cucurbita plants, that is, *Benincasa hispida, Lagenaria siceraria, Momordica charantia, Trichosanthes anguina*, and *Cucurbita maxima* was evaluated and compared with wheat fiber as control. The SCFA production by all four plants was found to be higher than that by wheat fiber using different probiotic strains.[171]

Conclusions

The triumvirate of fatty acids, polyphenols and prebiotics is an essential component of our diet and a balance in interplay among these leads to anti-oxidant, anti-inflammatory and immunomodulatory effects that are of high significance in both morbidity and mortality associated with COVID-19 infection. Their anti-diabetic nuances further render them even more suitable for consumption by diabetic people to reduce the risk of the complications of COVID-19. The concept of food synergy is widely reported wherein the phytonutrients in the presence of other phytoconstituents are believed to provide higher health benefits as compared to when they are administered alone.[172] This has been largely attributed to enhancement in the bioavailability of phytonutrients by interplay of biochemical, physiological and signaling factors. Therefore, consumption of various parts of plants belonging to the family Cucurbitaceae

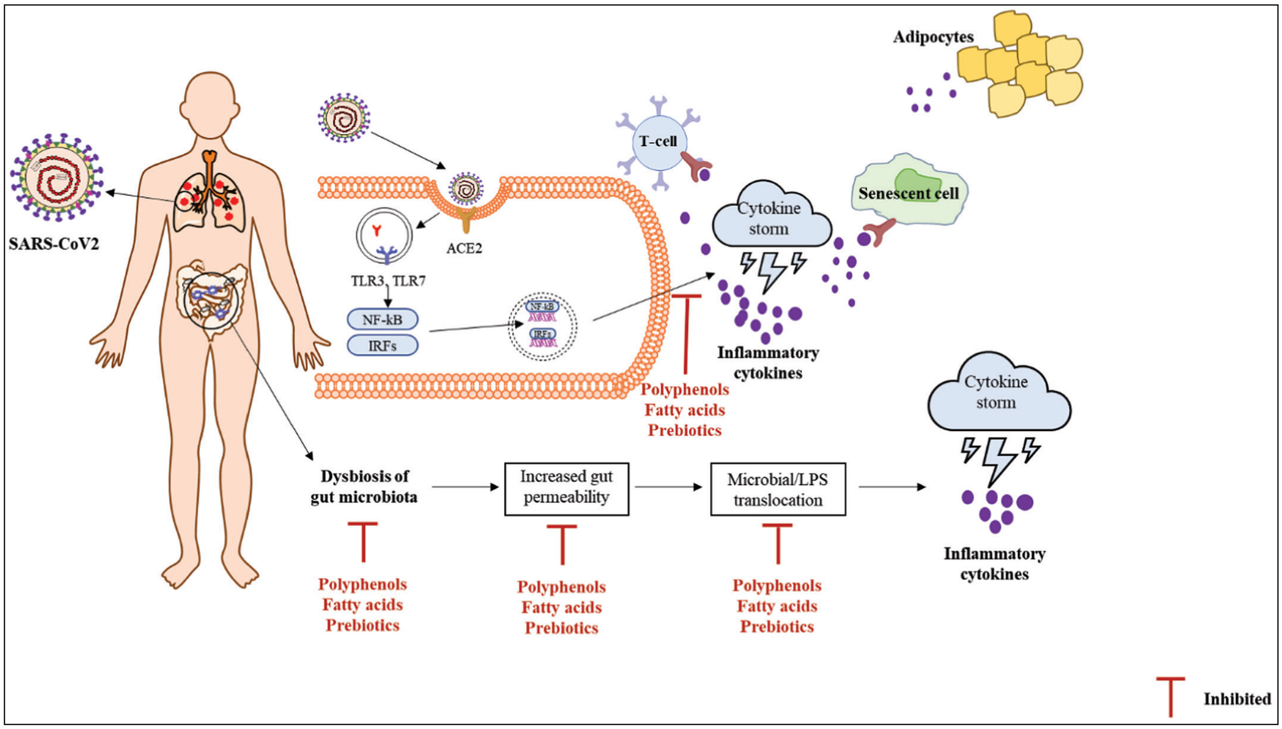


Figure 2: Pathophysiological events of COVID-19 leading to cytokine storm and the potential role of cucurbita phytoconstituents in attenuating the cytokine storm. ACE2: angiotensin I converting enzyme 2; TLR: toll-like receptors; NF-kB: Nuclear factor kappa B; IRF: Interferon-regulatory factors

may proves to be more effective as compared to consumption of the isolated nutrients. We conclude that certain cucurbita plants come across as convincing alternatives by regulating the production and release of proinflammatory cytokines, interfering with the development of the virus and modifying certain molecular pathways related to the pathophysiology. Though the nutraceutical role of the cucurbita plants has been extensively discussed, attributing these effects to specific phytotherapeutics has not been done due to lack of reports in this direction. Based on the fact, that COVID-19 has a plethora of symptoms varying from patient to patient in intensity, it is suggested to work further to elucidate the role of each class of compounds in combating the different symptoms. Such clinical studies will pave a way for making personalized dietary recommendations involving the inclusion of different cucurbita plants in patients manifesting different symptoms.

Looking at the formidable morbidity and mortality of COVID-19, we suggest that these plants should be rigorously tested to protect the COVID-19 patients, especially those belonging to the vulnerable groups.

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Conflicts of interest

There are no conflicts of interest.

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