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Benefits of dietary sesame seed and flaxseed to strengthen immune system during COVID-19 pandemic and prevent associated comorbidities related health risks

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Abstract

COVID-19 pandemic situation has created massive social and economic crisis globally and poses huge risks to survival of vulnerable, economically weaker groups, mainly in low-income and middle-income countries. Mortality appears to be high among persons with low immunity, poor nutritional status (malnourished) and associated comorbidities. Improve immune functions through nutrition is the most effective strategy to combat COVID-19 and other related viral infections. It is a long term process to improve immune power through a diverse and well balanced diet, but most significant during this unpredictable time when appropriate drug or vaccine is not available to prevent this viral infection. As strong immune system helps to recover any infectious disease conditions within a short period of time. This content is related to the link between nutrition, coronavirus disease 2019 (COVID-19), and the immune system. Main purpose of this content is to support the principle that diet rich in antioxidant and biologically active functional ingredients could be an effective nutritional intervention to restore the immune response, reduce inflammation and oxidative stress. Importance of flaxseed and sesame seed in the nutrition sector is because of their functional and highly active food ingredient. Those active food compounds have also health benefits against comorbidities in the COVID-19 patients including cardiovascular disease, hypertension, diabetes, cancer and various respiratory diseases. However, it is well established that due to influence of various nutritious components and bioactive molecules flaxseed and sesame seed playing critical roles in immune system. Daily dietary consumption of these foodstuffs helps to build up immunity against infectious disease and prevents COVID-19 related mild to chronic inflammations.

1. Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a positive-stranded RNA virus and transmitted through respiratory droplets. SARS-CoV-2 is easily attached to angiotensin-converting enzyme 2 (ACE2) receptors through spike glycoproteins, which is present on the envelope of the virus. ACE2 receptors are highly expressed by lung epithelial cells, cells of the heart, liver, bladder, gastrointestinal tract, kidney which makes them the main targets of the virus. One of the reasons for the higher infection rate among the adult population than children is the higher expression of the ACE2 receptors. Incubation period of this virus is around 3-7 days (ranging from 2-14 days). COVID-19 virus mainly affects respiratory system. Common clinical symptoms of this infection are fever, cough, breathing difficulties, and other nonspecific symptoms such as fatigue, headache, muscle

pain, dyspnea, digestive symptoms, vomiting, and diarrhea. Severe conditions ultimately lead to pneumonia, acute respiratory distress syndrome (ARDS), multiorgan dysfunction (Li *et al.*, 2020; Ouassou *et al.*, 2020). Optimal nutritional balance is one of the effective ways to prevent any type of viral infection including COVID-19, maintain immunity at the individual level. Nutritional intervention can improve well-being and control harmful health consequences such as diabetes, hypertension, and excess body weight/obesity. Negative nutritional status can increase the infection rate, viral load, mortality rate and delayed recovery from infections (Naja *et al.*, 2020). Nutritional modulation of the immune system is the most acceptable way to boost up immune system and suppress the infection progression rate during this pandemic situation (Derbyshire *et al.*, 2020). Functional foods have many positive effects like mitigating various metabolic, non-communicable and infectious diseases along with basic nutritive values. Polyunsaturated fatty acids (PUFAs), phytosterols, antioxidants probiotics, prebiotics, symbiotics are commonly known as functional ingredients (Granato *et al.*, 2020). According to the World Health Organization (WHO) and Centers for Disease Control and Prevention comorbidities such as cardiovascular diseases, diabetes, chronic respiratory disease, HIV, liver disease, renal disease, asthma, hypertension, obesity,

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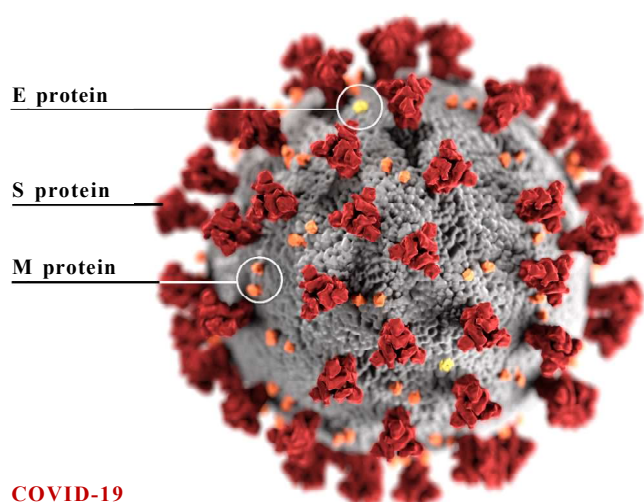
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cancer increases the COVID-19 (SARS-CoV-2) infection risk and shows poor clinical outcomes at the time of treatment. (Ejaz *et al.*, 2020; Guan *et al.*, 2020) (CDC, 2020) (WHO, 2020). Poor diet, unhealthy lifestyle, negative nutritional balance in the body are some common and major contributors to chronic metabolic, non-communicable diseases such as cardiovascular disease, obesity, type 2 diabetes and many others. Therefore, the most effective approach to manage infection related risk factors is the optimization of nutrient intake through nutrient dense food stuff along with good hygiene practices during food handling.



COVID-19

Corona virus - Photo credit: CDC/Alissa Eckert, MS; Dan Higgins, MAMS. (Source: Khan *et al.*, 2020: The COVID-19 pandemic: A scoping review.)

2. Immune response in COVID-19

Millions of people throughout the world affected by (SARS-CoV-2) during (COVID-19) pandemic. Low inflammation and oxidation stress are always associated with a healthy immune system. Imbalance among reactive oxygen, reactive nitrogen species (lipid peroxides, nitric oxide, singlet oxygen) endogenous and exogenous antioxidant activity resulting oxidative stress in the human body. Reactive oxidative species (ROS) can be produced and accumulated in the body due to endogenous antioxidant defense mechanisms which leads to oxidative stress. Immune cells like macrophages produce free radicals during infection and elevate oxidative stress consequently (Ntyonga-Pono M *et al.*, 2020). Cytokines such as interleukin-1 β , tumor necrosis factor- α (TNF- α), interleukin-6 are released due to onset of infection associated inflammatory stimulus, which ultimately mediate inflammation *via* activation of toll-like receptors (TLRs), TNF-receptor, IL-6 and IL-1 receptors (Iddir *et al.*, 2020). In SARS-CoV-2 infection, S glycoprotein present on the envelope binds with ACE2, which stimulate toll-like receptor-7 (TLR-7) and further secretion of inflammatory cytokines (IL-1, IL-6, MIP-1A, TNF- α , monocyte chemo attractant protein-1 (MCP-1), interferon 1 (IFN1). During SARS-CoV-2 infection also inflammatory markers like IFN- γ , IL-1 β , IL-4, MCP-1, IP-10 and IL-10 level increases because of systemic inflammatory responses. In case of ICU patients elevated concentration of IL-7, IL-2, IL-10, IP-10, MCP-1, granulocyte-colony stimulating factor (GCSF), TNF- α ,

macrophage inflammatory proteins (MIP-1A) are clearly noticeable in plasma (Fu *et al.*, 2020). Cytokine storm is very common during COVID-19 infection because of host tissue damage by innate immunity of the body. Cytokine storm is a result of chronic T cells stimulation and exhaustion, which decreases body defense mechanisms and puts the patient into a more dangerous situation. Cytokine storm further leads to accumulation of fluid within lung tissue, alveolar damage, lung injury and respiratory failure (ARDS) that is the main reason for death after COVID-19 infection due to diminished acquired immune response (lower amount of lymphocytes, CD8⁺ and CD4⁺) of the body. Decrease free radical oxidative stress (ROS) and inflammatory cytokines by supplying adequate antioxidant is one of the effective pathways to combat against COVID-19 infection related consequences (Calder *et al.*, 2020; Horowitz *et al.*, 2020).

3. Bioactive components of sesame seed

Sesame seed (*Sesamum indicum* L.) is known as the queen of oilseeds due to its unique property such as high oil content, flavor and aroma. Popularity of sesame seed is continuously increasing due to its various health benefits (Myint *et al.*, 2020) (Parsaeian *et al.*, 2020). Sesame (*Sesamum indicum* L.) is a member of Pedaliaceae family and *Sesamum* genus. Another name of sesame seed is Gingelly seed (Til) which is one of the widely popular edible oil in India. Composition of the sesame seed is dependent upon variety, various environmental factors, genetic variation, climate, harvesting time, cultivation and ripening stage. White, red or brown and black are most popular three varieties (Shamim *et al.*, 2019). Sesame is a good source of oil (Soxhlet extraction process) and seed extracted oil has moderate to high concentration of phytochemicals, phytosterols (400 mg/100 g) (Sachin *et al.*, 2018) (Pathak *et al.*, 2017). The oil content of sesame seed is ranging from 39% to 49% and protein content around 20% (mainly glutamic, arginine aspartic acid, methionine and tryptophan) (Dar *et al.*, 2019) (V. N. Gohil *et al.*, 2018) (Khan *et al.*, 2020). Sesame seed is a rich source of unsaturated fatty acids (83%-90%), mainly linoleic acid (37%-47%), followed by oleic acid (35%-43%), stearic acid (5%-10%), palmitic acid (9%-11%) and trace amount of linolenic acid also present in it (Pathak *et al.*, 2017). Besides macronutrients, sesame has also considerable amount of lignans (sesamin, sesamol), tocopherol, phenolics, flavonoids and minerals such as calcium, magnesium (182.47 mg/100 g of seed), phosphorous, iron (7.37 mg/100 g of seed), copper, manganese, zinc (4.47 mg/100 g of seed), magnesium and vitamin B1 (Pathak *et al.*, 2017) (Dar *et al.*, 2019) (Dravie *et al.*, 2020). Quality of oil extracted from black sesame seed is best and used for various medicinal purposes (Shamim *et al.*, 2019). Roasted sesame seeds used on the top of bread surface, desserts, salads cookies, breadsticks, ice creams, chocolates and mechanically hulled sesame seeds generally used in candies, sweet wholesome tahini, cakes, pastries, rolls, crackers in commercial bakeries. Refined sesame oil has high self shelf due to presence of antioxidants in it (Nagendra *et al.*, 2012). Oil bearing seeds shows higher concentration of protein than other cereals seeds (Salama *et al.*, 2015)

3.1 Antioxidant and anti-inflammatory activities sesame seed

Antioxidant properties are expected to contribute a better immune-system. Antioxidants have the ability to prevent free radical damage during increased oxidative stress, increase the number of T cell subsets, interleukin-2 production, natural killer cell activity (Uscogiuri *et al.*, 220). Sesame seeds possess significant antioxidant activity due to presence of tocopherols, polyphenols and lignans. Antioxidant properties of sesame seed and extracted oil are important to slow down the oxidative deterioration process of lipids within it, which ensures prolong shelf-life of the oil and its nutritional quality (Wan *et al.*, 2015) (Abirached *et al.*, 2020). Sesame lignans showed immunomodulatory and hypocholesterolemic effects especially when consuming with tocopherol (Nagendra *et al.*, 2012). The order of antioxidant activity of the three lignans is sesamol > sesamin > sesamol. Antioxidant effect of sesamol shows scavenging effects against superoxide anion ($O_2^{\cdot-}$), hydroxyl (OH^{\cdot}), hydrogen peroxide (H_2O_2), nitric oxide and related other oxidants due to the presence of hydroxyl group (Castro-González *et al.*, 2020) (Mahendra *et al.*, 2015). Sesamol is very effective antioxidant against lipid peroxidation, microsomal peroxidation and excess low density lipoprotein accumulation within circulatory system (Jayaraj *et al.*, 2020). Chandrakala *et al.* (2015) confirmed the anti-inflammatory activity (down-regulated proinflammatory cytokines) of sesame oil and sesamin by using low-density lipoprotein receptor knockout (LDLR^{-/-}) female mice (Narasimhulu *et al.*, 2015). Average tocopherol content of sesame seed is 292 µg/g. Specifically, *S. indicum* species have highest amount of tocopherol content around 339.44 µg/g. Gamma-tocopherol predominantly present within seed followed by alpha-tocopherol and delta-tocopherol (Martinchik *et al.*, 2011; Pathak *et al.*, 2014) (Kim *et al.*, 2020). Additionally, sesame seed and sesamin both are effective to increase hepatic gamma-tocopherol level (Hanzawa *et al.*, 2013). *In vivo* experiments on rat model showed elevated amount of tocopherol concentration mainly gamma-tocopherol in plasma and increased its bioactivity after consumption of moderate amounts of sesame seeds (Cooney *et al.*, 2001). Vitamin E (tocopherol) is potentially beneficial for its antioxidant, immunomodulatory effects which help to improve humoral and cellular immunity (T lymphocyte-mediated immune function), enhancing natural barriers against pathogen, phagocytosis, production of antibodies and lower respiratory tract infections in elderly. It also suppresses the production of inflammatory markers such as IL-6, and (TNF)-α after pathogenic invasion. For these beneficial roles it may be used against the COVID-19 virus and reduce the infection risk (Khorrami *et al.*, 2018; Lewis *et al.*, 2019; Jayawardena *et al.*, 2020; Jovic *et al.*, 2020; Akhtar *et al.*, 2020; Fernández-Quintela *et al.*, 2020).

3.2 Potential role of sesame seed in COVID-19

Addition of sesame seeds in our daily diet in various forms during this pandemic situation shows various health benefits (Kumar, 2020). Black sesame is also safe for dietary consumption during SARS-CoV-2 viral infection (Shirani *et al.*, 2020). *In silico* analysis confirmed natural antioxidants like sesamin can effectively inhibit SARS-CoV-2 activity through attaching and interacting with active site residue Cys145 of the SARS-CoV-2 virus, which leads to further

control of viral replication process (Pandey *et al.*, 2020). Numerous studies support the use of sesame oil to prevent viral infection rate due to its unique physical and chemical properties. These are low surface tension, high viscosity, antiviral activity, high-boiling point, and low hydrophobicity of mucosal surface. Nasal coating by Sesame oil gives large area of protective layer against viral attachment and due to its high boiling point (about 21°C) protective layer stays longer. Sesame oil can easily entrap infectious during breathing and decrease direct viral contamination at the entry point (Fan *et al.*, 2020). Nik *et al.*, (2020) explained the mechanism through which unsaturated fatty acid incorporation into the lipid membrane of the viral envelope and destabilized viral membrane bilayer. By following this method sesame oil may inhibit infection rate of coronavirus. Yan *et al.*, 2019 used human coronavirus 229E as a model coronavirus and stated that supplementation of linoleic acid (LA) and arachidonic acid (AA) significantly inhibited HCoV-229E virus replication. Apart from that Ayush guidelines for the COVID-19 also support the use of sesame oil for kavala or oil pulling and then warm water rinse to prevent infection risk (Ministry of Ayush, 2020).

4. Bioactive components of flaxseed

Flaxseed is a very popular and widely used plant based functional food. Flaxseed also known as linseed (*Linum usitatissimum* L.) and it belongs to the family Lineaceae. It is a rich source of lipids (~41%), protein (~22%), carbohydrates (~29%), and other essential micronutrients. It contains several essential minerals especially potassium (5600-9200 mg/kg), phosphorous (650 mg/100 g), magnesium (350-431 mg/100 g), calcium and sodium. Some minor components also present, those are cyanogenic glycosides, phenolics, trypsin inhibitor, phytic acid, linatine, phytoestrogens, vitamins, selenium, minerals, cadmium and cyclolinopeptides (CLs). Flaxseed oil is an excellent source of the omega-3 fatty acid (~73 % of total fatty acid) mostly α-linolenic acid (ALA) with typical level of above 50%. Bioavailability of α-linolenic acid is more when flaxseed is consumed in oil form rather than in whole one (Rodriguez-Leyva *et al.*, 2010). Polyunsaturated fatty acids, viz, eicosapentaenoic acid and docosahexanoic acid are formed from ALA. Little amount of monounsaturated fatty acids (~18%) and saturated fatty acids (~9%) are also present (Punia *et al.*, 2020). Flaxseed know as a 'superfood' due to its various health benefits including with tag of generally recognized as safe (GRAS), and significant percentages of ω-3 polyunsaturated fatty acids make it one of the most popular functional food. Significant level of flaxseed lignans (75-800 times higher than any cereals, legumes, vegetables and fruits) and fibers (around 35-45 %) also shows lots of health benefits. Flaxseed is the richest source of plant lignans. Seed coat contains highest lignans, mainly secoisolariciresinol diglucoside (SDG). These plant lignans further converted into their active form in human body by metabolism of gut anaerobic bacteria. Out of total fiber content two-third is in insoluble form (cellulose, hemicellulose and lignin) and one third is in soluble form (mucilage) (Kajla *et al.*, 2015; Dzuovor *et al.*, 2018; Sanmartin *et al.*, 2020). Generally people consume flaxseed as whole, milled, roasted and in oil form (Goyal *et al.*, 2014). Nowadays, they are widely used in ready-to-eat breakfast cereals, multigrain bread, biscuits, salad

dressings, crackers, and many other organic products. Excess consumption of saturated fatty acids leads to various metabolic disorders. In this situation flax-oil could be beneficial because substitution of saturated fatty acid with PUFAs (ω -3 and ω -6) protects against several metabolic disorders. Flaxseed improves immunity against viral infections along with manage cytokine storm and inflammatory mediators due to presence of ω -3 PUFAs (Szabó *et al.*, 2020; Thibault *et al.*, 2020).

4.1 Potential role of flaxseed in COVID-19

Long chain polyunsaturated fatty acids play an important role in human health and disease through modulation of inflammatory mechanisms and innate immune response. ω -3 PUFAs is an effective strategy to reduce the risk of viral infections if consumed in sufficient amount (0.5%-2% of total calories). ω -3 PUFAs also reduces excessive IL-6 level and ω -3 PUFAs derived protectins may suppress viral replication rate by blocking viral mRNA export (Messina *et al.*, 2020) (Akrami *et al.*, 2020). ω -3 PUFAs improve phagocytosis activity of macrophages and macrophage related innate immunity (Hirayama *et al.*, 2017) (Kumar, 2020) (Davanso *et al.*, 2020). It is established that ω -3 PUFAs suppress the nuclear p65 NF- κ B translocation and reduces NF- κ B activation. ω -3 PUFAs also inhibit ERK1/2 MAPK activation and COX-2 production. Many hospitals prefer omega-3 fatty acids enriched enteral nutrition therapy for the patients of ARDS. Zhu *et al.* (2020) showed ω -3 PUFAs in dietary flaxseed oil (FO) significantly reduce interleukin (IL)-1 β , (TNF)- α , IL-6, IL-17A, fasting blood glucose (FBG), glycated hemoglobin, blood lipid, plasma lipopolysaccharide and inflammation in diabetic rat. Ren *et al.*, proved by meta-analysis that flaxseeds and its derivatives can reduce C-reactive protein in obese populations. Zhang *et al.* stated that ω -3 PUFAs including protectin D1, which is used to prepare antiviral drugs, is one of the effective interventions for this novel virus, COVID-19. They also said that ALA might be an optional therapy for this novel virus. ω -3 PUFAs has immunomodulatory functions, which help to inhibit cytokines and (ROS) production. It can activate NK cells, T cells and enhance production of B cells, immunoglobulin (IgM) and ultimately strengthen the innate immunity (Chang *et al.*, 2020).

4.2 Effect of flaxseed to enhance gut immunity

Healthy immune system is always essential for survival against any kind of infection related health risks. Gut microbiome associated immunity has a major role to prevent onset of infectious chronic diseases and related poor outcomes. Gut-associated lymphoid tissue (GALT) is the major site of immune cells within the human body. Gastrointestinal tract is the largest immune organ in mammals and it contains trillions of micro-organisms including bacteria, viruses, archae, and fungi. Maintaining healthy gut microbiota profile through nutrition can improve immunity among healthy population, geriatric population as well as immune compromised patients. Faulty dietary habits, antibiotic exposure can reduce the amount of good gut microbiota. Gut barrier provides protection against pathogenic infections through intercellular tight junctions, epithelial, mucus (physical gut barrier), maintaining acidity, bile salts, and proteolytic enzymes (trypsin). Dietary probiotic and prebiotic supplementation improves gut health and

reduce gut inflammation. Plant based diet generally provides a nutrient diversity which is favorable for healthy gut microbiome. Probiotics are 'live micro-organisms, which, when consumed in adequate amounts, confer a health benefit of the host' and prebiotics are 'a substrate that is selectively utilized by host micro-organisms conferring a health benefit' (Childs *et al.*, 2019). 'Gut dysbiosis' leads to various chronic diseases like inflammatory bowel disease, type 2 DM, cardiovascular disease and many more. Even during old age gut microbiota diversity is reduced. Gut microbiota always support the functions and development of innate and adaptive immune system. Maintaining a healthy gut microbiome could be an effective way to reduce the chance as well as severity of the COVID-19 infection by maintaining the balance between anti-inflammatory (regulatory T cells) and pro inflammatory immune (Th17, IL-1, IL-6, TNF- α) responses. Beneficial gut microbiota shows antiviral activity by direct interaction with pathogenic microorganisms, secretion of antiviral substances, and modulating immune system. Even gut dysbiosis may contribute the clinical manifestation in the COVID-19. Gut microbiota secreted small amount of short chain fatty acids (SCFA) such as acetate, butyrate, propionate which possess various immunomodulatory (Dhar *et al.*, 2020) as well as anti-inflammatory properties (reduction of TNF- α , IL-6, IL-1 β). SCFAs have ability to activate the functions of immune cells including T lymphocytes, neutrophils, macrophages and dendritic cells and stimulate anti-inflammatory cytokine IL-10 production. Prebiotics are able to increase immunity through up regulating anti-inflammatory cytokines expression and down regulating pro-inflammatory cytokines expressions. Prebiotics supports the production of butyrate in lower gastrointestinal tract which is well for its anti-inflammatory functions during severe conditions in asthma and cystic fibrosis (Chaari *et al.*, 2020). Healthy gut microbiome also helps to alter lung immunity and modulate pulmonary immune system during infection through gut-lung axis. Beneficial gut microbiota improves local immunity (*via*, gut wall integrity) as well as systemic immunity by improving specific and non-specific immunity. Probiotics are effective to enhance innate immune system through improving phagocytosis activity and microbicidal functions of leucocytes; natural killer (NK) cells (Sundararaman *et al.*, 2020). Immunoglobulin A (IgA) secreted from subepithelial B-cells provides herd immunity and protection against enteropathogens (Chassaing *et al.*, 2014).

Flaxseeds are rich source of lignans mainly secoisolariciresinol diglucoside, which is 75-800 times more in these seeds than other fruits, vegetables, cereals grains, and legumes (Imran *et al.*, 2015). Both soluble and insoluble fibers such as cellulose, hemicelluloses, mucilage gums, and lignin are present in flaxseed. Gut microbiota ferment those dietary fibers (gum, resistant starch, inulin, pectin) and produces various (SCFAs) like acetate, butyrate, and propionate. Due to production of SCFAs, flaxseed used as a prebiotic which promote gut health by modulating intestinal microbiota and gut microbial environment (Zarepoor *et al.*, 2014). *In vivo* experiment in pig intestine showed flaxseed meal-containing diet (soluble fiber) enhanced microbial load (more than 2.2 log-folds) in the ileal digesta, mucosa and caecal mucosa of the pig models (Ndou *et al.*, 2018). Mohamed *et al.*, 2019 conducted an *in vivo* experiment

to evaluate the effect of flaxseed oil on the gut microbiota. They selected male adult albino rats (Western) strain for their experiment and divided them into four groups. First group treated with saline (control), second group received flaxseed oil (1 ml), third group treated with 1 ml flaxseed oil nanoparticles and last group received 2 ml flaxseed oil nanoparticles. They showed maximum bacterial count was with last group (received 2 ml oil nanoemulsion) compared to other groups. Various *in vivo* experiments confirmed the positive effect of dietary fiber against viral infection. Gut microbiota ferments dietary fiber into short-chain fatty acids which shows some anti-inflammatory functions. Dietary fermentable fiber supplementation and SCFAs production after fermentation promote both innate and adaptive immunity. Due to presence of high amount of both soluble and insoluble dietary fibers makes flaxseed are appropriate for gut health. Also soluble and insoluble fermentable fibers present in flaxseed helps to produce short chain fatty acids by gut microbiota and exhibit the growth and function of the healthy gut microbiota (Zhu *et al.*, 2020).

5. Effect of seed protein to prevent protein deficiency during infection

The human body requires protein one of the essential macronutrients for proper functions of the body. Protein deficiency can be a major problem in economically weak countries due to low availability, unhealthy dietary pattern with low nutrients, consumption of highly processed food or junk food, and poor absorption rate. Protein deficiency leads to high risk of infection including decreased immunoglobulins and gut-associated lymphoid tissue (gut-mucosal defense system) activity. Dietary intake of sufficient amount of protein associated with anti-inflammation. Protein rich foods with other essential macronutrients have potential to manage risk severity of viral infection. Protein requires for proper maintenance, nourishment and healing purposes of immune cells. In geriatric population protein supplement essential for maintenance of muscle mass, strength, and physical activity along with down regulate catabolic effects. Protein intake mainly from plant sources effectively reduces inflammation and oxidative stress and overall inflammatory burden (Hruby *et al.*, 2019).

Protein content of flaxseed varies from 10.5% to 31%. Approximately, 73.4% of total protein is globulin fraction and remaining 26.6% is albumin (Ganorkar, 2013). Flaxseed proteins are comparatively high in arginine, aspartic acid, and glutamic acid than other amino acids. Analysis of different kind of cultivars confirmed the existence of six essential amino acids (21.06-50.65% of total amino acids content) including methionine, threonine, valine, tryptophan, phenylalanine, lysine and nine non-essential amino acids (49.35-78.94% of total amino acids content) including glutamic acid, glutamine, aspartic acid, asparagine, glycine, cystine, proline, alanine, serine. The essential amino acids concentration and composition of flaxseed are same as present in soybean (Shim *et al.*, 2014; Kaur *et al.*, 2017). Although, plant based protein is not consider as complete protein and don not have high biological value due to absence of one or more essential amino acids but flaxseed protein contributes some health benefits to protein deficient malnourished populations and those who are dependent

on vegetable protein only (vegan or vegetarian population) and have milk protein intolerance and/or allergies. Gluten free flaxseed protein is safe for persons with gluten intolerance (Ganorkar, 2013). Flax protein isolates widely used as a nutritional supplementation to improve nutritional status and growth rate of infants with low birth weight due to presence of high amount of arginine and cysteine content. Analysis of amino acids profile of flax protein isolate showed lower ratio of lysine to arginine (0.25) than whey protein isolate (WPI) (5.38), sodium caseinate (2.15) and soybean protein isolate (0.71). Low lysine to arginine ratio of flax protein isolate is beneficial for cardiac health because it has little effect on various cardiovascular risk factors and vascular reactivity (Vega-López *et al.*, 2010; Kaushik *et al.*, 2016). Apart from nutritional value flax protein isolate shows antioxidant property also mainly in acidic media (Mohamed *et al.*, 2019). Bhatena *et al.*, (2020) showed positive effect of dietary flaxseed protein on plasma lipid profile of rat models. Rats (F344) with normal lipid levels and obese rats (SHR/N-cp) with elevated cholesterol and triglyceride were used for this experiment. They proved dietary flaxseed protein suppressed plasma triglyceride, cholesterol level and fat deposition in livers of the both rat strains compared to soy protein (Bhatena *et al.*, 2002).

Protein content in sesame seed varies between 18-25% (Oduma *et al.*, 2020). Out of the storage protein content globulins present 67.3%, followed by albumins (8.6%), glutelins (6.9%) and prolamines (1.4%). Defatted sesame seed shows protein content upto 50%. Sesame seed contains various amino acids such as arginine (140 mg/g protein), leucine (75 mg/g protein), methionine (36 mg/g protein), cystine (25 mg/g protein) and moderate amount of lysine (31 mg/g protein). Soybean protein is deficient in methionine (16 mg/g protein) but high in lysine content (68 mg/g protein), so that mixed diet with both soybean and sesame seed protein may be a good option to optimize nutritional value and protein quality (Namiki, 2007). After oil extraction procedure of sesame seed, remaining residue part (sesame seed meal) become an excellent source of protein (Baghban-Kanani *et al.*, 2019). Sesame protein isolate can be used as a supplement to enrich amino acids content and improve nutritional compositions. Sesame protein isolate contains highest amount of glutamic acid among all the amino acids, followed by aspartic acid. Total amino acid content is 95.70 g/100 g sesame protein isolate. Due to high protein digestibility and amino acids content sesame protein isolate supplementation could be a healthy way to reduce protein deficiency related health consequences especially in developing countries (Fasuan *et al.*, 2018).

6. Regulating COVID-19 associated comorbidities

Individuals with non communicable diseases like diabetes, hypertension, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), malignancies, HIV, and many others comorbidities are more prone to get COVID-19 infection compared to healthy individuals with healthy immune system. Comorbidities put anyone to a life-threatening situation during SARS-CoV-2 infection. SARS-CoV-2 virus attached with ACE-2 receptors for viral transmission. Some comorbid conditions strongly linked with ACE-2 receptor over expression. Comorbidity also stimulates the

release of proprotein convertase which exhibit the viral transmission chance into the host cell. Moreover, comorbidities delay the outcome procedure and increase severity, mortality rate during COVID-19 infection [48]. One meta-analysis across mainland China showed 25.1% of the total positive patient (1590) had single comorbidity and 8.2% had more than one during admission. Commonly registered comorbidity was hypertension (16.9%), followed by diabetes (8.2%) [49]. One more meta-analysis (1576 COVID-19 infected patients) again confirmed that hypertension (21.1%), diabetes (9.7%) 95% CI: 7.2-12.2%), cardiovascular disease (8.4%), and respiratory system disease (1.5%) were the most prevalent comorbidities among hospitalized COVID-19 positive patients (Yang *et al.*, 2020). 856 hospitalized COVID-19 positive cases investigated in China which showed hypertension (16.6%) was the common comorbidity followed by diabetes (7.5%) (Ye *et al.*, 2020). Study conducted on patients with COVID-19 infection investigated that severe comorbid condition leads to poor recovery outcome and prolong hospital stays associated with ICU admission, mechanical intubation and death. Through managing these most prevalent comorbidities we can reduce the severity of COVID-19 infection as well as control fatal events (Nandy *et al.*, 2020).

Sesame seed extracted oil may control blood glucose level of persons with type 2 diabetes by activating hepatic antioxidant enzymes like superoxide dismutase, glutathione peroxidase and catalase. Sesame oil has positive on blood glucose level of type 2 diabetic individuals. Experiment was conducted on forty-six participants with type 2 diabetes. After 90 days of experiment, it was clear that sesame oil increased insulin level, hepatic antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) activities and lowered the HbA1c level, thiobarbituric acid reactive substances as well (Aslam *et al.*, 2019). Study on 60 type 2 diabetes mellitus patients concluded that combination of sesame oil and glibenclamide had more significant anti hyperglycemic effect (36% reduction of blood glucose level, and 43% reduction of HbA(1c) compared to single therapy with only sesame oil. This combination therapy may be an effective and safe for further clinical practices in the field of hyperglycemia (Sankar *et al.*, 2011). Ramesh *et al.* (2005) confirmed the positive effect of sesame oil on diabetic rats. They showed reduction of blood glucose along with reduced glycosylated hemoglobin level, and increased glucose-6-phosphatase, fructose-1,6-bisphosphatase, hexokinase enzyme activation compared to control diabetic rats (Ramesh *et al.*, 2005). Sesame seeds significantly reduce both systolic and diastolic blood pressure of hypertensive persons due to its antioxidant lignans (sesamin, episesamin, sesamol and sesamolol), fatty acids and vitamin E content (Cardoso *et al.*, 2018). Use of sesame oil blend (20% unrefined lignans rich sesame oil with 80% refined γ -oryzanol-rich rice bran oil) as a cooking oil for 60 days provided significant blood pressure (systolic, mean arterial, diastolic) reduction in mild-to-moderate 400 hypertensive patients. Study group treated with both sesame oil blend and nifedipine showed maximum blood pressure reduction after experiment (Sankar *et al.*, 2015). A meta-analysis with 843 participants provided evidenced that Sesame consumption directly associated with both systolic and diastolic

blood pressure reduction (Khosravi-Boroujeni *et al.*, 2017). Long term daily consumption of sesame oil increased endothelia functions of hypertensive men (Karatzi *et al.*, 2013). Wichitsranoi *et al.* (2011) stated that black sesame meal decreased systolic BP, oxidative stress and improved vitamin E status. They selected 22 pre-hypertensive women and eight pre-hypertensive men for 4 weeks for their experiment (Wichitsranoi *et al.*, 2011). Consumption of sesame oil significantly reduce body weight and body mass index also (Alipoor *et al.*, 2012).

Flaxseed based products also effective to low both Systolic and diastolic blood pressure of hypertensive persons due to rich source of dietary α -linolenic acid, lignans, and fiber. A meta-analysis with 1302 participants suggested that supplementation with flaxseed products inhibited both systolic and diastolic blood pressure among selected participants. Diastolic blood pressure reduction was visible after flaxseed powder and flax-oil supplementation but in case of flax-lignans effect was not visible (Ursoniu *et al.*, 2016). In another meta-analysis (11 studies) also supported the fact that flaxseed supplementation reduced both systolic and diastolic blood pressure. Consumption of whole flaxseed for more than 12 weeks was more effective to maintain diastolic blood pressure (Khalesi *et al.*, 2015). Flaxseed derived products like flax oil, flax lignan complex, secoisolariciresinol diglucoside, flaxseed protein hydrolysate also have direct effect on blood pressure reduction. Flaxseed, flax oil, and flax lignan can reduce blood pressure in hypertensive humans, and remaining secoisolariciresinol diglucoside, flaxseed protein hydrolysate shows positive effect on sprague dawley rats and spontaneously hypertensive rats (Prasad, 2019). Clinical trial on 80 hyperlipidemic and hypertensive patients showed flaxseed can reduce anthropometric measurements such as waist circumference, Waist to hip ratio and lipid profiles of individuals after daily consumption of 36 g of flaxseed for 8 weeks (Haghighatsiar *et al.*, 2019). According to many human and animal studies flaxseed supplementation significantly decreases diabetes. One study investigated that flaxseed enriched yogurt (200 g yogurt with 30 g flaxseed) can control hyperglycemic condition (decreased hemoglobin A1c level), lipid profiles (reduced triglycerides and total cholesterol) and blood pressure (SBP and DBP) in type 2 diabetic individuals after 8 weeks of daily consumption (Hasaniani *et al.*, 2019). ω -3 fatty acids supplementation is essential during gestational diabetes mellitus because of its satisfactory positive effects on fasting plasma glucose, insulin resistance, insulin levels and insulin sensitivity (Jamilian *et al.*, 2020). Flaxseed gums also very effective to maintain blood glucose and cholesterol level in the human body (Thakur *et al.*, 2009).

Cardio protective effect of dietary antioxidants with flaxseed and α -tocopherol were confirmed by using high fat fed diabetic golden Syrian hamsters (Haliga *et al.*, 2015). Flaxseed based diet effective against obesity related risk factors also. Many clinical studies confirmed its effectiveness. 45 Randomized clinical trials suggested that flaxseed supplementation helps to reduce body weight, BMI and waist circumference. Subgroup analyses found a significant reduction in body composition after long term consumption of whole flaxseed body composition. So that whole flaxseed could be a good option for weight reduction diet (Mohammadi *et al.*, 2017).

Another randomized controlled trial performed on 68 patients with non alcoholic fatty liver disease for 12 weeks observed significant blood glucose and fat mass reduction after 12 weeks supplementation of flaxseed (Rezaei *et al.*, 2020). One more clinical study found that sesame oil decreased systolic and diastolic blood pressure to normal level but again it increased when participants stopped sesame oil consumption. This study was conducted on 32 male and 18 female patients for 45 days and each participant used sesame oil as an edible oil throughout the study period. Reduction in body mass index, body weight, lipid peroxidation also noticed after the experiment (Sankar *et al.*, 2006)

It is now well establish fact that COVID-19 infection is strongly associated with cardiovascular diseases. Preexisting cardiovascular disease may prolog hospital stays and poor outcomes. Further it leads to severe stage of COVID-19 infection and ultimate death. Even COVID-19 infection can cause various severe cardiac problems such as arrhythmia, myocardial injury, acute coronary syndrome and venous thromboembolism. Reduced physical activity during lockdown can be a risk factor for cardiovascular during this pandemic situation (Nishiga *et al.*, 2020). 21 observational studies on 77317 hospitalized COVID-19 positive patients revealed that cardiovascular risk factors or comorbidities positive associated with high mortality rate among hospitalized patients. Out of the total hospitalized positive cases 12.86% had cardiovascular comorbidities and 14.09% showed cardiovascular complications during hospitalization period (Sabatino *et al.*, 2020). Highly sensitive troponin level was observed 8-12% of all infected patients, which determined acute cardiac injury. Systemic inflammation and myocardial injury during COVID-19 infection were the major risk factors for cardiac disorder and associate health risks (Bansal, 2020).

Experiments on human and animal models stated that sesame seed and extracted oil both are very promising substances to control high cholesterol level, atherosclerosis, cardiovascular consequences and related inflammations due to presence of antioxidant and anti-inflammatory properties. It is very effective way to reduce low-density lipoprotein (LDL), triglycerides levels as well as maintain high-density lipoprotein (HDL) levels in human body. Lignans (sesamin and sesamol) present in sesame seed have hypocholesterolemic and antioxidant effects (Hsu *et al.*, 2017). Clinical randomized trial on 48 patients showed daily sesame oil (daily 4 table spoons) consumption for one month significantly reduced cholesterol, triglyceride, low density lipoprotein level, body Weight, waist measurement among participants. Sesame oil intake also elevated high density lipoprotein (HDL-C) level after the experiment (Namayandeh *et al.*, 2013). One more experiment on high fat fed rabbit model clearly indicates that sesame oil supplementation can improve serum lipids profile (Asgary *et al.*, 2013). Mainly in case of vitamin E, alpha-tocopherol and gamma-tocopherol are most significant in CVDs. Singh *et al.* (2007) conducted double blinded parallel study and showed gamma-T supplementation significantly reduce risk of thrombotic events and platelet activity by controlling lipid profile (Singh *et al.*, 2007). Sesame derived sesamin can reduce the severity of endothelial dysfunction, atherosclerotic lesion, vascular inflammation and thrombosis by exhibiting NO bioactivity and decreasing the ROS

production in blood vessels (Dalibalta *et al.*, 2020). Food-based polyphenol is very active to control several cardiovascular diseases including oxidative stress related atherosclerosis, *via* stimulating Nrf-2 chemical signaling pathway and further reduction of foam cell formation on endothelial lining (Jayaraj *et al.*, 2020). Daily administration of two different doses of sesame oil (5 and 10 ml/kg body weight) for one month provided significant protection against isoproterenol induced oxidative myocardial damage. Male Wistar albino rats were used for this experiment. Chronic sesame oil administration offered defense mechanism by suppressing thiobarbituric acid reactive substance, glutathione, catalase, superoxide dismutase and elevating endogenous antioxidant enzymes. Those mechanisms ultimately reduced oxidative myocardial injury and oxidative stress (Saleem *et al.*, 2013). Experiment on Swiss albino mice model with hyperlipidemia showed that administration of 50 and 100 mg/kg body weight of sesamol not only significantly controlled cholesterol and triacylglycerol level of the mice model but also reduced the absorption rate of cholesterol as well (Kumar *et al.*, 2013). To develop natural cardio protective drugs Sesame lignans could be a good option in future (Eweda *et al.*, 2020).

Flaxseed is well known cardioprotective food due to its high amount of ω -3 fatty acid (alpha linolenic acid), lignan and fiber. Bioactive compounds have anti-inflammatory, antioxidative properties (Rodriguez-Leyva *et al.*, 2010; Parikh *et al.*, 2019). *In vivo* experiment on novel rabbit model revealed that dietary flaxseed supplementation is very much effective against atherosclerotic plaque formation (approximately 40% reduction). Along with this decrease in NF- κ B and proliferating cell nuclear antigen (PCNA) expression in vascular tissue also clearly visible after flaxseed supplementation. Alpha linolenic acid (ALA) helps to suppress atherosclerosis progression through inhibiting oxidation, inflammation and cell proliferation into vascular tissue (Francis *et al.*, 2013). Another *in vivo* experiment by using LDLrKO mice model showed lower plasma cholesterol and saturated fatty acids level after supplementation of 10% (wt/wt) ground flaxseed with cholesterol-enriched diet. Flaxseed supplementation with cholesterol exhibited plasma level of alpha linolenic acid and decreased plaque formation in the aorta and aortic sinus compared to only cholesterol fed mice. Dietary flaxseed supplementation reduced atherosclerosis risk in mice model due to anticholesteremic, antiproliferative and anti-inflammatory actions. Flaxseed based dietary supplement also stabilized various inflammatory markers like IL-6, mac-3, and VCAM-1 along with proliferating cell nuclear antigen (PCNA) expression (Dupasquier *et al.*, 2007). Micro RNAs (miRs) including miR-1, miR-29b, miR-133a, miR-133b, miR-135a are associated with cardiac remodeling processes after myocardial infarction (MI). Flaxseed oil modulates miR-133a, miR-135a, and miR-29b and shows cardioprotective effect in MI due to presence of high amount of alpha linolenic acid content (Parikh *et al.*, 2020). Experiment on 40 male albino rats showed positive effect of flaxseed on acute myocardial ischemia after 6 weeks oral supplementation. Exercise training combined with flaxseed supplementation significantly elevated HDL level as well as antioxidant and anti-inflammatory paraoxonase 1. IL-1 β , Cardiac

troponin, and TNF- α level decreased among flaxseed supplementation treated group compare to group with myocardial ischemia (Nounou *et al.*, 2012). One randomized double-blind, placebo-controlled trial on 60 diabetic patients with coronary heart disease showed flaxseed oil supplementation for 12 weeks (1000 mg ω -3 fatty acids from flaxseed oil) can modulate gene expression level of IL-1 and TNF- α , lipoprotein (a), and PPAR- γ (Hashemzadeh *et al.*, 2017). Flaxseed oil supplementation can reduce overactive endocannabinoid system associated coronary artery disease (Saleh-Ghadimi *et al.*, 2020).

7. Conclusion

Now the COVID-19 pandemic is the most severe threats to health and the economy globally. As of now, there is no permanent and strong cure strategy to eliminate this novel infection, alternative methods need to be accepted to control the infection spreading. The inclusion of certain functional foods in our daily diet to maintain healthy immune system is not a final cure strategy for COVID-19 infection. Healthy lifestyle and eating patterns may optimize the immune system function and control the further progression of the infection into a severe state. Sesame seed and flaxseed consumption for a long time not only mitigate infection risk but also help to prevent malnutrition related health problem to some extent. Functional components of these oilseeds can control and inhibit co-morbidities related health risks. Moreover adequate dietary intake may be essential to protect against inflammatory response to SARS-CoV-2 infection, and preventing and improving its outcome.

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Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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