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### Abstract

**Background:** To evaluate the potential of probiotics in stress management caused by the Covid-19 pandemic. **Materials and Methods:** PubMed, Elsevier, New England journal of Medicine and Google Scholar were searched for the keywords “Probiotics and stress management during the Covid pandemic” up to 30th April 2022. **Result:** Probiotics have a great potential of managing mild stress. The pandemic has brought about physical as well psychological distress and has had a negative impact on the mental health of individuals. Stress increases the risk of cardiovascular diseases, hypertension and neuropsychiatric disorders. Probiotics can be used to alleviate mental stress. Probiotics maintain ecological balance of gut and provide immunity. They also affect mood and health of host by regulating gut-brain axis of host and may be used as Psychobiotics by altering various neurotransmitters like dopamine, serotonin, adrenocorticotrophic hormone, epinephrine, norepinephrine and GABA. The use of probiotics in mild stress will help reduce the risk of adverse effects and dependence associated with the psychotropic drugs. **Conclusion:** The ongoing studies on probiotics seems to be a good solution towards stress and related problems which is rapidly increasing due to COVID-19 pandemic. Probiotics seem to be beneficial in handling stress as they alter the release of neurotransmitters reducing stress level of an individual and have a positive effect on mood. The current pandemic is likely to continue and there is a need for greater preparedness of stress management, therefore, it is essential to explore the full potential of probiotics application in stress management.

## INTRODUCTION

Coronavirus was first seen in city of Wuhan, China. COVID-19 is a highly contagious disease which is caused by the acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus strain. World Health Organization (WHO) declared coronavirus as pandemic on March 11, 2020. Mild illness in humans include common cold while more lethal viruses can cause severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS) and COVID-19.<sup>[1]</sup> Fever, cough, tiredness, shortness of breath, loss of smell, loss of taste, aches, sore throat, difficult breathing are some symptoms of COVID-19.<sup>[2,3,4]</sup> Also the coronavirus pandemic associates considerable degree of fear, concern, stress in the population which is the root cause of many other problems. The virus can be transmitted by respiratory droplets, aerosols and by fecal-oral contact. Thus virus has enforced dramatic changes to daily lives including economic and health status.<sup>[5]</sup> The pandemic is associated with both physical and psychological distress and is

having negative effect on mental health of the society. All over the world, people are aware regarding the physical outcomes of coronavirus infection and measures taken to prevent exposure to coronavirus. However, the effects of pandemic on mental health of an individual and on approach to avert stigmatization is currently ignored. Interpretation of the epidemiology, clinical features, pattern of transmission and its management is major area of concern. This is because all are facing challenges that can be stressful and can cause strong negative emotions. Pandemic causes anxiety, disruption, stress, xenophobia and stigma of an individual or society. The long term consequences continue to affect children and adolescents also. They are facing many challenges including no offline schooling, lack of communication with friends and teachers and child abuse has also increased. It has been indicated that children and adolescents experience sleep problems, anger issues, nightmares and anxiety. The disruption in normal life increased stress among adolescents. There are many surveys which suggest that the pandemic has

increased the stress in people. In one of the study done in the United states on mental health of college students suggests that of the total of 195 students 71% i.e. 138 student are suffering with increased anxiety and stress because of COVID-19 outburst.<sup>[6]</sup> Another study under the aegis of the Indian Psychiatry Society in which an online survey was conducted and total of 1871 responses were collected, of which 1685 responses were considered and analyzed. According to this about two-fifth had anxiety and three-fourth of the participants reported moderate level of stress.<sup>[7]</sup> These surveys confirm that the problem of psychological distress is increasing many folds and the pandemic causes not only physical but also has great negative impact on mental health of an individual. Since, social distancing is necessary to prevent spread of COVID-19 but the practice can make us feel isolated, lonely and can increase psychological distress. Young people generally do not have much past experience to deal with stressful conditions, thus they pose a greater threat of mental health problems during COVID-19. Therefore, effect on younger generation is much worse because of lack of certainty and the long-term problems which will have negative emotions on an individual later in life. Thus, the pandemic leads to destruction at many levels for the adolescent generation. However, during this COVID time it's alarming to take care of mental health of an individual. These are some factors which are responsible for causing more mental stress in lives of people during pandemic.

### 1. Mechanism/Pathophysiology

It has similar pathogenic action as that of SARS-CoV. The virus comprises two types of spike protein (S protein) all over its membrane which helps it in binding with the host cell an Envelope protein (E protein) and Membrane protein (M protein) forms the capsid of the virus. Single-stranded positive RNA is the genetic material of this virus.<sup>[8,9,10]</sup> SARS-CoV2 also uses Angiotensin-Converting Enzyme 2 receptors of type 2 cells of alveoli like SARS-CoV for interaction with host cells. Transmembrane protease serine 2 (TMPRSS2) is needed for S protein priming. There are two types of S protein i.e. S1 and S2 which participate in binding and fusion respectively. S1 binds with the ACE2 receptor while S2 mediates fusion between virus and host cell.<sup>[11]</sup> Once the virus enters the host cell it shreds its protein part and RNA is released into the cytoplasm. The SS (+) RNA uses host mechanism to translate into two polypeptides i.e. PPa1 and PP1ab which form a replication transcription complex. Further, the formed complex uses RNA dependent RNA polymerase to replicate and make multiple copies. Finally, it gets assembled into its virion vesicles and fuses with plasma membrane and gets released. It spreads down the bronchial tubes and starts infecting neighbour cells. The accumulated proteins of virus, dead type 2 cells of alveoli attract macrophages and cytokines as an immune response

and result in inflammation. This further results in the filling of lungs with water and dead cells causing acute respiratory disease.

### 2. COVID-19 relation and problems with Psychological distress

- Headache, body pains, stomach problems and skin rashes are commonly seen physical problems due to decreased immune responses.<sup>[12]</sup>
- Feelings of anger, fear, sadness and concentration problems leading to more usage of substances like tobacco and alcohol.<sup>[13]</sup>
- Worsening of mental health conditions like depression or even suicidal thoughts.<sup>[14]</sup>
- Psychological stress is used as pessimistic emotional experience. However extreme psychological stress has extremely negative consequences on an individual's physical and mental health. More psychological stress increase the risk of diseases like, cardio vascular diseases,<sup>[15]</sup> hypertension,<sup>[16]</sup> digestive system disorder,<sup>[17]</sup> and neuropsychiatric disorders. This leads to reduced happiness in lives of people. A diagrammatic representation was presented in [Figure 1].

Thus finding an effective method to relieve stress in an individual, and society is significant topic of research in medical field nowadays. The use of probiotics seems to be beneficial in handling stress as they alter the release of neurotransmitters reducing stress level of an individual. The ongoing studies on probiotics seems to be a good solution towards stress and related problems which is rapidly increasing due to COVID. The purpose is to explore the role of probiotics in stress management.

### 3. Probiotics

Probiotics are living microbes that, when administered in adequate amounts, confer a benefit to the health of the host.<sup>[18]</sup> The beneficial role of probiotics is demonstrated in [Figure 2]. They are live beneficial bacteria or yeasts that are good for an individual. Probiotics are generally regarded as helpful bacteria because they maintain health of gut. They are known components of functional foods. The human body especially the digestive system, naturally contains probiotics which are useful bacteria. Lactobacillus and its different strains are used as most common probiotic which can help with diarrhea and to people with Lactose intolerance i.e. people who have difficulty in digesting lactose. Fermented foods and yogurt are generally rich in beneficial microbes. Also, Symptoms of Irritable Bowel Syndrome (IBS) may be reduced using Bifidobacterium which is a constituent of dairy products. Probiotics are used to improve normal flora of gut and digestion. They are generally used to manage irritable bowel, urinary tract infections, diarrhea, vaginal yeast infections, eczema and lactose intolerance.<sup>[19]</sup> Probiotics are certainly active

microbes. When they are given in sufficient quantity they play a role in maintaining ecological balance of the gut. Probiotics also have a stimulating effect on the host's immune system. They act on the cells involved in natural immunity and specific immunity and in activation of macrophages. Also, probiotic microorganisms stimulate antibody production, especially immunoglobulin A (IgA) in the lumen of intestine. This can prevent the adherence of pathogenic bacteria to the mucosal surface.<sup>[20,21]</sup> But the benefits of probiotics are many more, they have a great potential to be used as mental stress reliever. The role of probiotics is not limited to gut but they also do play a major role in mental health of an individual. Some of the studies have found that immunity and endocrine are ways of probiotics to regulate nervous system functions and mood. Synthesis of certain neurotransmitters can be increased or decreased using probiotics. Levels of neurotransmitters such as, brain derived neurotrophic factors, serotonin, cortisol are affected thus reducing the stress level of an individual. Since probiotics have positive effect on mood, and psychological processes they can be termed as Psychobiotics. These may be used as an alternative for stress related mental health problems.

#### 4. Probiotics as Psychobiotics

The diet of an individual gradually influences the mental health. New researches revealed an extensive bidirectional communication network between gut and brain. Probiotics seems to play a beneficial role in stressed population. According to a research low socioeconomic group is more vulnerable to depression as their diet consists less amount of fermented foods and probiotics. The mild psychological distress may be improved by use of probiotics. Probiotics have become increasingly popular in recent years. One should take lot of probiotics food, such as yogurt or take daily probiotics supplement to reap their potential benefits. Nowadays, psychobiotics i.e. probiotics for treating various mental health conditions are being widely studied and it reveals that they are helpful in alleviating psychological distress to certain extent by altering neurotransmitters.<sup>[22]</sup>

Some of the proposed microorganisms which have the potential to act as psychotropic agents includes *Streptococcus thermophiles*, *Lactobacillus acidophilus*, *Lactobacillus lactis*, *Clostridium butyricum*, *Bifidobacterium bifidum*, *Bifidobacterium lactobacillus*, *Bacillus coagulans* and many more. These are different strains of probiotics which are generally found in gut and alike supplements. However the advantageous results on health of probiotics are specific to species and strain. In respect to mental health many strains of *Bifidobacterium* and *Lactobacillus* are extensively studied which shows positive effect on mental health as compared to species like *Streptococcus* and *Bacillus*. Also, the gut-brain axis is affected by *Lactobacillus helveticus* and *Bacillus*

*longum*. But the drawback is that combination of strains is generally used which makes difficult to segregate the microbes strain or strains which are most beneficial to alleviate mental stress. Further scope of research is to isolate more strains which may have productive effect on mental health.<sup>[23,24]</sup>

#### 5. Mechanism of action

Psychobiotics are the class of probiotic bacteria with great potential to alleviate mental stress related problems by (i) Producing and expressing neurotransmitters that may affect appetite, mood and sleep habits (ii) Response to stress conditions (iii) Reducing inflammation in your body as inflammation can contribute to depression. Various rodent studies show that consuming probiotics prevents stress induced release in corticosterone, adrenocorticotrophic hormone (ACTH), adrenaline and noradrenaline. These are the markers of stress and their significant reduction suggests that probiotics reduce the activity of hypothalamic-pituitary adrenal axis. In patients suffering with depression this axis is hyperactive.<sup>[25,26]</sup>

People who are suffering from extreme stress have decreased levels of BDNF i.e. Brain derived neurotrophic factor. Consumption of probiotics leads to increased expression of these factors. BDNF plays a role in the pathophysiology of stress-related disorders. The BDNF is responsible for brain plasticity, memory and neuronal health.<sup>[23]</sup>

Probiotics work by reducing levels of pro inflammatory cytokines in brain and decreases stress. The intake of these bacteria in diet can help production of norepinephrine, acetylcholine, dopamine, serotonin, cholecystokinin glutamate which are essential in behavioural regulation and functions associated with Central nervous system. It is also involved in bidirectional gut brain communication through hormonal, metabolic and neural pathways. The neurons of enteric nervous system interact directly with the neurochemicals produced by microbes of the gut thereby influencing the messages to central nervous system.<sup>[28]</sup>

Probiotics possess both antioxidant and free radical scavenging activities which leads to increase absorption of nutrients and increase production of gamma amino butyric acid (GABA). These are implicated in depression pathophysiology. The oral administration of Gamma Amino Butyric Acid derived from fermentation of *Lactobacillus hilgardii* have clinical importance in reduction of anxiety as shown by preliminary studies.<sup>[29,30]</sup>

Also, the intake of microbe specific probiotics lead to free production of tryptophan which leads increased availability of serotonin. 5-hydroxytryptamine (5-HT) or serotonin is a neurotransmitter which is biosynthesized in both gastrointestinal tract and central nervous system from tryptophan i.e. an essential amino acid. In gastrointestinal tract it is involved in gastrointestinal motility and intestinal secretions whereas it is involved in regulation of emotions, stress, sleep and

appetite in central nervous system thus alleviating symptoms of psychological distress. Number of living organisms called as CFU i.e. colony forming unit are the basis of dosing of probiotics. For instance *Bifidobacterium infantis* treats irritable bowel syndrome and it requires 108 CFU for beneficial effect. Dosing of probiotics depend on indication for what it has been prescribed. Research is lacking for effective dosage of various species and need to determine the dosage of different strains which alleviate stress in population.

## 6. Psychobiotics versus Psychotropic drugs

Thus probiotics exhibit multidirectional benefits. They reduce stress which is very important for healthy mental health of an individual. Probiotics are not the alternative to psychotropic drugs as probiotics help in reducing stress and anxiety and is not associated with treatment of severe depression. But definitely, probiotics are nowadays need of an hour as many people are suffering from mild stress in their daily lives and this stress is increased due to COVID-19. Probiotics is not only essential for gut but also reduces stress and has minimal or no side effects. Use of probiotics than psychotropic drugs in dealing with mild stress cases is better. Metabolic and endocrine side effects are often linked with usage of psychotropic drugs for alleviating mental health diseases as treatment option. Thus the adoption of alternatives with minimal side effects to the human body are essential which needs urgent consideration. The main advantage of using psychobiotics in controlling mental health problems is that they are the microorganisms which belong to gastro intestinal tract thus if compared to psychotropic drugs they may present less dependence and decreased risk of allergies.<sup>[31,32,33]</sup>

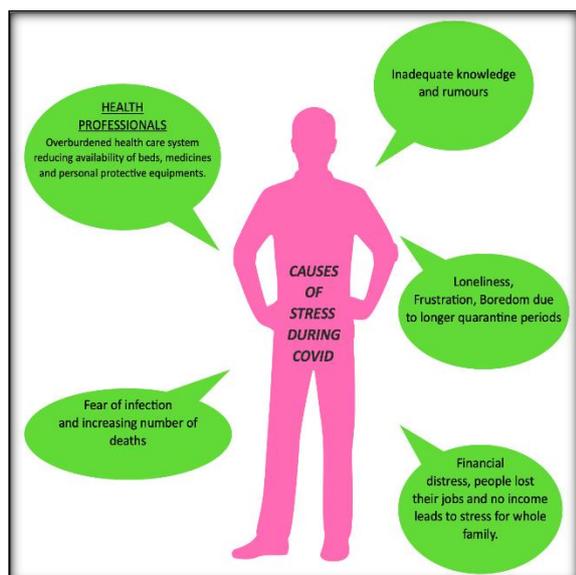


Figure 1: Causes of stress during COVID-19

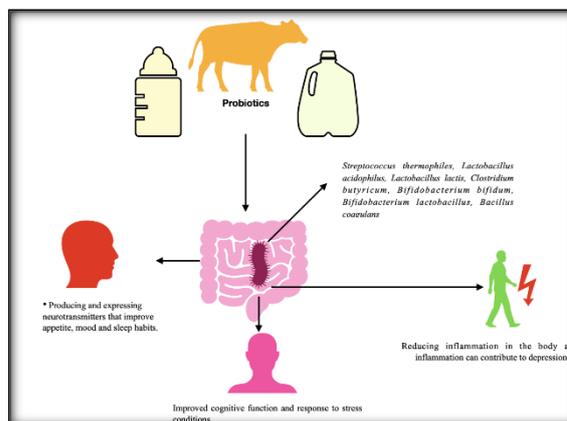


Figure 2: Beneficial role of probiotics

## CONCLUSION

COVID-19 has led to vigorous and multifaceted responses. As the pandemic continues to increase, the challenge of dealing with stress also increases. The current pandemic is likely to continue and the need for greater preparedness for stress management is essential. The scientific evidence support the usage of probiotics in nutrition to yield health benefits. Probiotics increases growth of beneficial gut microbes. Improvement of stress related psychiatric problems like anxiety by modulation of gut brain axis has stressed upon the importance of probiotics. Probiotics affect mood and health of host by regulating gut-brain axis of host. Thus, probiotics are of great potential in dealing with mild stress and other mental conditions. Thus more researches should be done in exploring full potential of probiotics in this aspect. Probiotics application in stress management will increase to great degree with current process of research.

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