International Journal of Pharmaceutical and Phytopharmacological Research (eIJPPR) | June 2020| Volume 10 | Issue 3 | Page 139-146
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COVID-19 Outbreak in Terms of Viral Transmission and Disease Biocontrol by Healthy Microbiome

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ABSTRACT

Before the end of December 2019, thousands of pneumonia cases were recorded. The causative agents of these strange symptoms were unknown. These cased started in Wuhan, Hubei Province, China. At the beginning of January 2020, a new virus was detected in throat swab samples of patients who suffering from fatigue, heat more than 38◦C, dry cough, dyspnea, and lung pain. The presence of sputum, headache, hemoptysis, diarrhea, nausea, and vomiting were not common symptoms. The isolated novel virus resembled that of the coronavirus and was named coronavirus 2019 or COVID-19. In February 2020, the cases of human COVID-19 infections were increased and spread all over the world. The number of reported deaths and positive cases increased daily in China, the USA, the Middle East, Europe, and South Asia. COVID-19 like the six previously studied and isolated coronaviruses that cause severe human pneumonia with a high mortality rate. The zoonotic corona virus-like COVID-19, acute respiratory syndrome (SARS- CoV), and the Middle East respiratory syndrome (MERS-CoV) are infectious and develop strong respiratory damage and pneumonia. The viral genome of COVID-19 was extracted and sequenced. It contained about 29, 903 nucleotide bases and the phylogenetic study revealed that it is similar by 89.1 % to SARS-like coronaviruses. These nucleotide similarities clarify the high activities of COVID-19 in human infection. All retrospective studies showed that COVID-19 is dangerous and can spread quickly between human beings. Thus prevention of infection may be important. This review deals with the prevention of COVID-19 infection using different methods. The Gut microbiome is a common group of probiotics with promising benefits health effects in humans. They antagonistic some bacterial pathogens and enhance the immunity of the host. They may process valuable antiviral effects and decrease respiratory tract infections, viral counts, and help critically ill patients. The actions of probiotics as antiviral may be indirect through stimulation of the immune system. Activities of probiotics against viruses were not studied sufficiently and lack in information or data is noticed. Some of these probiotics are found in the gut and intestinal tract. Native gut microflora improved and enhanced the host immune system to react more rapidly to detect different pathogens. Studies on the effect of probiotics type, dose on viral population infections at different ages, and viral development are urgently needed. Also, the antiviral effects of the probiotics and their mechanisms of actions are necessary to be studied and explained. In conclusion, probiotics may protect against viral infection and may aid in avoiding COVID-19 infection and developments through helping our immune system to strongly fight viruses.

Key Words: *Corona recedes, gastrointestinal tract, microbiota, microbiome, Probiotics, respiratory infections, COVID-19.*

eIJPPR 2020; 10(3):139-146

HOW TO CITE THIS ARTICLE: Mona O. Albureikan (2020). "COVID-19 Outbreak in Terms of Viral Transmission and Disease Biocontrol by Healthy Microbiome", International Journal of Pharmaceutical and Phytopharmacological Research, 10(3), pp.139-146.

INTRODUCTION

The last ongoing global health crisis obtained by COVID-19 is a very dangerous catastrophe threatens the world. Continued human to human transmission has been reported leading to infection of many healthcare workers [1]. Although most cases of COVID-19 have been associated with fever and respiratory symptoms [coughing, shortness of breath, and pneumonia], mild or subclinical cases cannot be ruled out. Little information about transmission mode, clinical presentation, or the extent of spread was recorded. Infections by this virus ranged from mild syndrome to fatal complications like pneumonia, the collapse of different organs, and a cytokine storm syndrome leading to changes in gastroenterology [1-3]. People with inflammatory bowel disease have increased intestinal ACE2 appearance which

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 21 March 2020; **Revised:** 03 June 2020; **Accepted:** 05 June 2020

may increase COVID-19 susceptibility [4]. During COVID-19 infections, dealing with immune- suppression and immune modulation patients is difficult and needs immune cell activation using the Gut microbiome.

The gut microbiome is important for developing human immunity and there is a strong relationship between benefit microorganisms and epithelial cells which tolerated antigens and pathogenic bacteria [5, 6]. Toll-like receptors [TLRs] from the membrane of the epithelial and lymphoid cells of the small intestine are involved in this differential recognition, being responsible for the normal development of the intestinal mucosal immune system. TLRs suppress the occurrence of an inflammatory response and promote immunological tolerance to normal microbiota components. The role of TLRs is to recognize different general microbe-associated molecular patterns e.g., peptidoglycan components, muramic acid, capsular polysaccharides and lipopolysaccharides, flagellin, and unmethylated bacterial DNA [7, 8]. After stimulation, signals are initiated to activate B cells [NF-kB], genes of chemokines and cytokines, and immune response [9, 10] but inhibit inflammatory reactions and are necessary to keep intestinal homeostasis [11].

Viral Infection of the Human Respiratory Tract

Viral infections are considered as one of the principal threats to human life and health worldwide [12-14]. Large varieties of etiologic agents or viruses are widespread among mammals and birds. This group of viruses mainly caused the global outbreak and human morbidity and mortality worldwide due to respiratory tract infections. More than 200 infectious viruses infect the respiratory tract especially that named rhinoviruses and contained 150 serotypes, causing acute upper tract infections were reported [15]. Also, Coronaviruses are the commonest etiological agents that infect the respiratory system and cause diseases that had social and economic bad impacts due to the high costs of hospitalizations and medical care in addition to loss work [16]. More than US$40 billion/ year were in the USA due to common colds viral infections [17]. Another group is human enteroviruses which cause respiratory tract infections ranged from gentle to strong respiratory symptoms up to pneumonia [15]. Consequently, other groups of viruses that attach upper and lower respiratory tract and cause severe infections are influenza viruses, respiratory syncytial virus, adenoviruses, parainfluenza, and coronaviruses [18-20]. New molecular methods helped to added different numbers of viruses that cause respiratory illness such as coronavirus which increased morbidity and mortality [21]. Recently, the novel virus that attracts respiratory tracts like human bocavirus, metapneumovirus, and the new coronaviruses HKU1, NL63, and COVID-19 were reported [4, 22, 23].

Corona Virus Recedes:

Many reports showed the possibility of the COVID-19 virus to go into the human cells using glycoprotein spikes [S protein] which attached to the ACE2 receptor which is highly expressed on pneumocytes of the lower airways leading to increasing pneumonia rate in patients [23-25]. Corona recedes may be one of the following two scenarios. The immunity in people's bodies increased as a result of infection with the virus and no symptoms of varying severity appeared on most people or by the discovery of a vaccine for prevention or a drug for treatment. Any other scenario for the end of the current situation in any country will not be a virus recedes but it is an exposure of people who have not been infected in the past or have not been exposed to a risk of infection one day. In the future if any country announces the green light for the return of life to normal quickly will be dangerous. The virus will not die and the world will not be able to face it again in the next winter. Scenario number 1 is the only safe way for the virus strikes in a second coming wave. The solution to protecting ourselves from being exposed to infection during virus strikes is staying home. The policies of countries to return to normal must be gradual, planned, and not immediately or quickly. Formation of antibody [a previous infection] or receiving a vaccine would be one of the conditions for obtaining human protection in the future for all countries.

Avoidance of the Respiratory Viral Infections:

Nowadays, the avoidance of infections of the respiratory system by any viruses is a problem due to the lack of new antiviral agents or vaccines that inhibit virus infections or developments. Even partially, vaccines of influenza or adenoviruses are accessible but for other virus groups no effective therapy is recorded up to date. There are two problems that the world is facing. The lists of viruses that infect the respiratory tract were increased every year and their resistance to drugs or antiviral materials was increased. To control the hazard viral infections effective drugs or vaccines must be developed and used. Alternative medicine therapy is an important and safe way to prevent or control bacterial, viral, or fungal infections.

Respiratory virus infections such as common cold and COVID-19 caused increased morbidity and economic losses and prevention of these infections have a good impact on reducing illness and improve human health [25]. The use of Probiotics or their products may solve a part of the respiratory virus infection problems. Since the relationship between viral replication and gastrointestinal immunity is very close, an effective approach over probiotic bacteria can play an important role in stopping viral replication [26].

COVID-19 and Digestive System:

Some studies reported that COVID 19 may strongly affect the Gastrointestinal tract because symptoms like diarrhea, nausea, and vomiting are noticed. In a pilot study, out of 651 infected cased of COVID 19, 11% of patients had nausea, vomiting, or diarrhea. Severe infection of COVID-19 was more clearly found in people with gastrointestinal tract troubles (23%) and 8% in healthy people meaning that COVID-19 might increase mucosal cytokine production which causes diarrhea [3] or COVID-19 host was more sensitive to electrolyte changes. A recent study in >100 (30%) outpatients with mild symptoms of COVID-19 had diarrhea which may due to direct infection of intestinal cells [2,3]. The gastrointestinal tract cells express the COVID-19 receptor [ACE2]. The viral infection led to nucleocapsid protein expression and viral spread from infected cells to new cells in the gastrointestinal tract and there are numerous infiltrating plasma cells and lymphocytes of the host indicating mucosal immune cell activation [1]. Possible fecal-oral transmission route of COVID-19 was recorded due to the presence of viral RNA in patient faces [1].

Probiotic Bacteria, Types and Importance

Some bacterial genera of human microbiota had considering beneficial effects and different health benefits by enhancing human immunity. They are living microorganisms, named probiotics because they live in association with the host [27]. The most common bacteria are that belonging to genera *Lactobacillus* and *Bifidobacterium*, found mainly in fermented products. Other genera of bacteria such as *Bacillus*, *Escherichia coli*, *Enterococcus*, and *Streptococcus* may improve human health due to the beneficial effect. These probiotics are characteristic by survival, growth multiplication, and production of useful material to benefit the host, live in a positive relationship with the host, and inhibit the host pathogens [28, 29]. Many studies reported that the presence of probiotics inside the gastrointestinal region benefits the host immune system and gut mucosa in addition to prevent acute diarrhea and allergy in children [30]. The most interesting benefit effect of probiotics is their inhibitory effects on specific viral infections where they reduced infection or severity and duration of the decrease. Their roles in biocontrol of rotavirus gastroenteritis infection were studied before [31] and many scientists suggested probable effective roles in biocontrol of respiratory tract viral infections by un-indefinite pathways [32]. Scientific information reported the possible role of probiotics to inhibit the SARS-CoV-2 virus and/or in the current COVID-19.

Human Microbiota:

In a healthy state, the human body carried more than 1000 type of different microbial flora belonging to bacteria, viruses, fungi, and cellular animals which found on or in the human body. the genes inside these florae are called the microbiome and each human carry many thousands of these microorganism cells which live associated with the human body in a symbiotic relationship. This microbiome represents 2-3% of the host dry weight. These microbiomes are concentrated on the gut, small and large intestine skins, mouth and vaginal, and genitals. There is a great diversity of microbiome between the different regions and the numbers and diversity of microbiome differed from person to another.

Gut Microbiome:

Gut contained different essential microbiota called Gut microbiome which found in huge diversity and affect host homeostasis and immunostains. The gut microbiome is associated with good human health and excellent development of the immune system and played vital roles in host immunity and susceptibility to diseases in addition to the deal with hypersensitivity, autoimmunity, inflammation, viral infection and cancer [33]. A gut microbiome is a huge number of bacteria, fungi, archaea, and protozoans live together in a symbiotic relationship with their hosts [34, 35]. Their numbers may reach 10^{14} cells from 2,000 species and 12 unlike phyla and their types differed from person to person and were affected by host genetics, age, sex, immunity of the host, habitude, diet, activities, and food types [27, 36]. Human consummation of yogurts or dietary supplement products daily enhanced the numbers Gut of healthy people contained specific genera that differed from the sick person who had its types of bacteria [37, 38]. The Gut microbiome consists of three types, floating flora in lumen, adherent flora to a mucus membrane, and adherent flora to the epithelial cell surface [39]. Gut microbiome may initiate before, during or after born from the mother vaginal tract microbiome [30] and human milk contained more than 10^9 bacterial cells/l in addition to some prebiotic oligosaccharides that encourage the development of *Bifidobacterium* and *Lactobacillus* but synthetic milk enhance the pathogenic Enterobacteriaceae growth and development [40]. Breast-feeding contained give bacteria, lysozyme, IgA, lactalbumin, lactoferrin, polysaccharides, fatty acids, and extra molecules [27]. Interestingly, death rates of babies due to intestinal and respiratory infections were reduced in breast-fed infants due to the presence of lactoferricin which is an effective antibiotic [41] while synthetic feeding stimulates growth enterococci and enterobacteria [41, 42].

Gastrointestinal Tract Microbiome:

Gastrointestinal Tract contained many Gut microbiome that can live in this environment and the types may belong to 17 families, 45 genera, and over 1,000 species bacteria [43-45]. Every part of the tract contained specific microbiota which differed between parts [46]. This gut microbiome or microbial ecosystem played many significant functions for the human host, like protection against pathogens, nutrient processing, stimulation and modulation of intestinal immune response and regulation of host fat storage [47].

The gastrointestinal tract of humans can be divided into three anatomical regions, Stomach, Small intestine [includes duodenum, jejunum, and ileum], and large intestine. The bacteria can request nutrients from the epithelial cells as necessary. Microbial induced signals between different bacterial species in cell-cell communications and played a significant role in the balance of their environmental niche and this tract contained the largest proportion of the human microbiota specifically the colon [48]. The gut microbial ecology had several important functions for the human host and act as a defense line against pathogens, help in nutrient processing, stimulation, and modulation of intestinal immune response and regulation of host fat storage [47]. The latest study also exposed that the bacterial populations of the gut, which modify quickly after birth, can adapt brain developmental pathways [49]. The content of the normal colonic microbiota is itself somewhat proportionately in fecal samples [48]. The colon considers a human sewage system, which also stores and removes the waste material from the Gastrointestinal tract and recycling water. The contents of the gut microbiota can be modified by changes in diet. However, we currently know that the GI tract is one of the most metabolically and immunologically dynamic organs of the human body.

The upper Gastrointestinal tract is occupied mostly by some acidic gram-positive bacteria such as *Lactobacilli* and *Streptococci* (10^2-10^4 cells/ ml [48]. The small intestinal tract contained large quantities of nutrients, carbohydrates, food components, and harbors large numbers of microbes. Microbiota in the jejunum look-alike the microbiota of the duodenum, there are bacteria of the genera *Bacteroides*, *Lactobacillus,* and *Streptococcus,* and the yeast *Candida albicans* [50]. Though, the profusion is higher and is up to 107 cfu/g. Likewise is in the ileum, although except *Bacteroides* and *Lactobacillus*, bacteria belonging to genus *Clostridium*, *Enterococcus*, and *Veillonella*, and the family *Enterobacteriaceae* are too prevailing [51].

The large intestine is a continuation of the ileum and is usually divided into three regions, the colon, rectum, and anal canal. The colon accounts for nearly the full length of the large intestine and colon compacts and eliminates about 100 ml/day of feces [52]. Microbiota of these parts is much more diverse and larger than the population of the upper part. The accumulation of GIT microbiota lives in the colon – their richness arrives at 10^{12} cells/g of luminal content [53].

Colon and rectum contain the biggest number of microorganisms population comparing to other regions [46]. The large intestine is populated by 800 species belonging to nine types of bacteria and one type of Archaea [50]. Among the nine bacteria types, two types are prevailing, *Firmicutes* (46-60%) and *Bacteroidetes* [with *Actinobacteria,* 8-28% [44]. In the colon about 270 of 800 species, belong to those two types [50]. Most of the colonic microbiota are obligate anaerobic bacteria, counting *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Enterococcus*, *Eubacterium*, *Fusobacterium*, *Peptococcus*, *Peptostreptococcus,* and *Ruminococcus* [54].

Source of Gut Microbiota in Gastrointestinal Tract:

Gut microbiota plays a significant role in human health. The number of bacterial cells in the human GIT is ten times more than the number of human body cells in total [47, 53]. Firmicutes (46-60%), Proteobacteria (10-30%), Bacteroidetes and Actinobacteria (8-28%) were isolated from Gastrointestinal tract [44, 46]. There are three subdivided bacterial communities within the normal microbiota in the human Gastrointestinal tract containing the upper part, ileum, and colon. At the beginning of life, the human Gastrointestinal tract is occupied by microbes that increase the digestion and immune system response [43, 55].

During the natural birth, the infants get mummies microbiota, both vaginal and fecal 45]. In the case of breast-fed infants 60-90% of the bacteria belong to genus *Bifidobacterium*, less to *Bacteroides* and *Lactobacillus* [50]. The digestive system of children is populated by bigger amounts of *Bifidobacterium* and *Clostridium* than the gastrointestinal tract of adults [50]. Also, the intestinal microbiota of children is much less complex [56]. In the adult human gut microbiota Bifidobacterium, Bacteroides, Clostridium, and Eubacterium dominate less compared to genera *Lactobacillus, Escherichia, Enterobacter, Streptococcus,* or *Klebsiella* [50]. Main bacterial species are only 30% of microorganisms in the human gut, the remaining 70% are unique microorganisms [44].

Autochthonous and Allochthonous Microbes:

Gut microbiota is divided into autochthonous microbes [residents] and allochthonous microbes [travelers]. Autochthonous are these often in symbiotic with human organisms, they are present in the normal adult's gastrointestinal tract. It also plays a role in maintaining the constant bacterial populations in the gastrointestinal tract and colonize particular parts of the tract. The autochthonous microbes can live aerobically as well as colonizes their habitats sequence in infants. Often relate closely with the gastrointestinal mucosal epithelium [52].

Allochthonous microbiota is passing microbes that reach the habitat in food, water, or comes from another habitat in the body [52]. These microbes are not found or they find it very difficult due to weak competition or might be killed by a host, or other bacterial factors. Allochthonous microorganisms might colonize the habitats occupied by autochthonous microbes in the troubled gastrointestinal system because of diet and other environmental factors [50].

Travelers compete with residents for colonization [45, 57]. About 70% of Gastrointestinal tract microbiota is considered to be variable [53]. Therefore, the main difference between the two categories is that an autochthonous microbe logically colonizes the habitat, while an allochthonous one cannot colonize it under irregular situations [58]. In a stable gastrointestinal ecosystem, all the niches are perhaps full by indigenous microbes [52].

Functions of the Gut Microbiota:

Gut microbiota takes energy through carbohydrate fermentation of indigestible dietary residues such as plant cell walls, fibers, and oligosaccharides which is the main function of gut microbiota [43,59,60]. They obtained energy, mainly through producing short-chain fatty acids that are absorbed and used by the host. Microbial fermentation also produced hydrogen, carbon dioxide, and methane gases [48] which affect gut physiology. Some gut microbiota also produced vitamins, B, and K. Moreover, the hydrolysis of urea to ammonia by the gut microbiota is important in recycling nitrogen in the intestine [48].

Gut Microbiome that Antagonistic Pathogenic Microbes:

The microbial fermentation in the human colon formed three main Short-Chain Fatty Acids in addition to acetate, butyrate, and propionate. Diet and microbial composition in the gut may affect the produced molecules [59]. The gut microbiota has a protective role against pathogenic microorganisms cascade under two mechanisms, colonization resistance and stimulation of immune function [48]. The local microbiota efficiently inhibits the founding and/or overgrowth of harmful bacteria in a healthy state. Also, convinced numbers of the intestinal microbiota are motivating immune function both locally and systemically [60-62]. Interactions between the mucosal wall, normal microbiota, and gut-associated lymphoid tissue are dominant to the host protection against pathogenic attack and infection [48]. The three-component system is integral to the equilibrium of the Gastrointestinal tract ecosystem and mounting an immune response. Such changes make an irregular immune response to external antigens [allergens and pathogens], and even their intestinal bacteria [46].

The protective function has been confirmed by tests accepted out on animals with a sterile digestive tract [germ-free], which were more liable to infection [43, 46, 63]. Also, they suffered from reduced vasculature bodies, lower activities of digestive enzymes, and lower levels of epithelial lymphocytes [63]. Intestinal bacteria that are harmful to the human host have enzyme activities that differ from those of microbiota [64]. Increasing numbers *Bacteroides* and *Clostridium* spp. and decrease *Bifidobacteria* destroy human intestinal gut flora and may cause colorectal cancer in some patients [65, 66].

Using a suitable amount of vegetables, fruits, nuts, whole seeds, and useful olive oil and low proteins improve gut microbiome diversity and reduce inflammation. Also eating a wide range of plant-based foods, rich in the fiber-enhanced gut microbiome and human health. Additionally, yogurt, cheeses, and milk products are a true and excellent food that contained live and active bacterial cells [probiotics] in life forms. Alcohol, cold drinks, cakes, antibiotics, and sugars increased numbers of bad flora and decreased the growth of useful gut microbiome.

Prevention of Respiratory Virus Infection with Probiotic Bacteria:

Lung and respiratory tract infections by a virus which is enveloped negative-sense RNA virus [family Paramyxoviridae] showed mild or severe symptoms in children, adults, or older [67-69]. Symptoms may be mild as common colds or severe in babies and in people who suffered from severe diseases or low immunity [70-72]. Prevention or biocontrol of these types of human infection is needed [73, 74] reported an interesting role for lactic acid bacteria especially *Lactobacillus gasseri* which played important roles and had many functions like avoidance of influenza A viral infection in animals, reduction of adipocyte size and increased lifespan in *Caenorhabditis elegans* [a free-living transparent nematode]. This previous bacterium showed inhibitory activity against the respiratory syncytial virus which cause a dangerous disease. After rat treatment with these bacteria, viral counts decreased by time while no significant differences in rat weight were recorded. Also, the increased pro-inflammatory cytokines expression after viral was lower after treatment with *Lactobacillus gasseri* compared to control [untreated with bacteria]. Furthermore, interferon and interferon expression genes in addition to SWI2/SNF2-related CREB-binding protein activator protein [SRCAP] were induced by the presence of *Lactobacillus gasseri* which suppressed the viral activities. A clear relationship was found between viral infection development and the SRCAP expression where SRCAP protein is viral non-structural bind proteins. The addition of therapeutic agents in the human diet may act as a deterrent drug [73, 75] and until now no useful treatments or successive respiratory virus vaccines were recorded [76]. Therapeutic drugs against human viruses are needed to be used to control the coronavirus recedes. The inhibitory effect s of natural killer T-cells against influenza virus was increased after treatment by *Lactobacillus acidophilus* L-92 while *L. acidophilus* NCFM walls enhance antiviral gene expression in animals [77, 78]. *Lactobacillus gasseri* may have a role in the treatment of respiratory diseases caused by viral infection through induction of TNF-α factors and type I and II IFN which may defend against viral infection [79-81]. Many results showed that *Lactobacillus gasseri* enhanced IFN-β and IFN-γ expression at the gene level in the lungs of mice after RSV infection and several lactic acid bacteria induce IFN-β or IFN-γ in the lungs of mice infected with a respiratory virus to contribute to virus clearance [82, 83]. From all discussed information probiotics may have excellent roles to control viral infection through indirect ways which must be discussed in the future.

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