

NIGELLA SATIVA, NATURAL HONEY, PROBIOTICS AND PARAPROBIOTICS: COULD THEY HELP IN THE TREATMENT OF COVID-19 INFECTION?

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ABSTRACT

Coronavirus disease-2019 (COVID-19) pandemic emerged in December 2019 resulted in extreme demand for treatment. This review summarizes the potential effect of nigella sativa, natural honey, probiotics and paraprobiotics in the treatment of COVID-19.

At the end of 2019, a group of pneumonia patients of unknown cause emerged in Wuhan China.^[1] Subsequently, the World Health Organization (WHO) announced a standard format of Coronavirus Disease-2019 (COVID-19), according to its terminology, for this novel coronavirus pneumonia on February 11, 2020. The symptoms of COVID-19 infection may appear between two to fourteen days after the incubation period.^[1] Currently, no treatment has been proved to be efficient in the treatment of infected patients by COVID-19.

Nigella sativa

Nigella sativa is belonging to the family of Ranunculaceae. Its popular name is black seed. Nigella sativa is an important medical plant contains a lot of active constituents as thymoquinone (30%-48%), p-cymene (7%-15%), Indazole alkaloid as nigellidene, alpha hederin, thymol, alpha pinene, isoquinoline alkaloid, triterpine and saponine which is anti-cancer agent, in addition to carbohydrates, crude fibers, protein.^[2] Nigella sativa is considered as a miracle herb because it has a lot of pharmacological activities mainly due to presence of thymoquinone as a bronchodilator, immunomodulatory, gastroprotective, anti-inflammatory, antioxidant, diuretic, antihypertensive, anti-diabetic, analgesic, hepatoprotective and antimicrobial agent.^[3] Therefore, Nigella sativa is used in the treatment of bronchitis, asthma, and to buttresses immune system.^[4]

Natural honey

Natural honey is not only food with very native value, but also it is considered very effective medicine in the

treatment of different diseases. Honey is very viscous liquid consists of different compounds like sugar, protein, carbohydrates in the form of glucose or fructose, vitamins, amino acids, minerals, and other compounds.^[5] Honey is very effective as anti-inflammatory, antioxidant, antibiotic, anti-cancer and anti-bacterial through changing the PH of the media or change of enzyme activity. Honey also is effective in the treatment of throat infection, bronchial asthma, and the prevention of cough.^[6] Natural honey has been considered a good alternative for antiviral drugs for the treatment of some viral infections.^[7] Honey has been previously considered as an alternative for acyclovir in the treatment of herpes simplex virus 1 (HSV-1), and it also demonstrated for its significant antiviral effect against varicella-zoster virus (VZV).^[8]

Probiotics and Paraprobiotics

Probiotics are living microorganisms involving bacteria and yeast, which, when administrated in adequate amounts, confers a health benefit on the host.^[9] Many types of bacteria can be used as probiotics, but most of them come from two groups: Lactobacillus and Bifidobacterium strains. However, the microorganisms that commonly used as probiotics are lactic acid bacteria (LAB); particularly, Lactobacilli Streptococci, Pediococcus, Enterococcus, Bifidobacteria, and some yeast as Saccharomyces boulardii.^[10] Paraprobiotics (ghost probiotics) are sterilized probiotics. Probiotics and paraprobiotics have different routes of administration e.g., oral, topical, and vaginal.^[11]

Site of action

The mechanisms by which probiotics act on the immune system are not clearly understood, especially at the molecular level. The proposed action of probiotics can involve different areas in the body. Probiotics can either interact with gut commensal bacteria or directly have a metabolic action producing some enzymatic activity at the intestinal level. Probiotics can interact with mucosal epithelium and enhancing its immune system as well as the efficacy of its mucosal barrier. On the other hand, administered probiotics can enhance the immune functions beyond the gut to the liver, lung, bronchi ...etc.^[12] Probiotics have immune-stimulatory role through mediators such as lipoteichoic acid, peptidoglycan, and nucleic acid.^[13]

Mechanism of action

Both innate and acquired immune systems are known to be enhanced by probiotics and paraprobiotics, so they can minimize the severity of infections, especially in the upper respiratory tract.^[14] Also, paraprobiotics were reported to maintain their immunomodulatory effect beyond their viability.^[15] *L. lactis* JCM5805 is one of the probiotic bacteria that can activate plasmacytoid dendritic cells (pDCs) to produce their antiviral effect. pDCs can detect the presence of viruses or bacteria by using certain Toll-like receptors (TLRs). Specifically, they use TLR9 to recognize microbial nucleic acids via detecting unmethylated CpG motifs of DNA, and TLR7 for the recognition of microbial RNA or synthetic guanosine analogs. Then production of type 1 interferons (IFNs) occurs as a result of pDCs activation by ligand binding to TLRs. *L. lactis* JCM 5805 is mainly taken up by pDCs, and its DNA extracts strongly induce IFN production. These observations suggest that the phagocytosis of *L. lactis* JCM 5805 by pDCs plays a vital role in activating such immune cells and stimulating IFN production via TLR9/MyD88 signaling. Interferon- α plays a vital role in mediating the antiviral immune response by inducing the cytotoxic activity of natural killer cells, which contributes to the host defense against viral infection.^[16]

Efficacy of *Nigella sativa* and natural honey against COVID-19

Nowadays, there are many clinical trials currently running to study the efficacy of *Nigella sativa* and natural honey against COVID-19.^[17,18] That's because honey is considered as a first choice in the treatment of acute cough caused by infection of the upper respiratory tract, which is currently a cornerstone symptom in COVID-19. Honey also can be a good treatment of fever, inflammation, throat infection, diarrhea, which are considered some of the suggestive symptoms of COVID-19.

Nigella sativa acts as a bronchodilator, antiviral, and support the immune system.^[19] There is another clinical test say that Nigellidine and alpha hedrine that present in

Nigella sativa can Inhibit viral replication so can be the best potential in the treatment of COVID-19.^[20]

Efficacy of Probiotics and Paraprobiotics against COVID-19

Previous studies showed that *Lactobacillus* and *Bifidobacterium* strains could decrease the severity and the duration of respiratory tract viral infection.^[21,22] Additionally, a systematic review identified 23 trials involving 6269 children found that probiotic consumption may decline the incidence and illness duration of respiratory tract infection attack.^[23] A recent study documented that proper nutrition and application of prebiotics and probiotics in patients with COVID-19 can prevent secondary infection.^[24] Previous studies showed that probiotics (*Lactobacillus rhamnosus* GG, live *Bacillus subtilis*, and *Enterococcus faecalis*) given to critically ill patients on mechanical ventilation developed less ventilator-associated pneumonia.^[25,26] However, the efficacy of probiotics in the reduction of mortality rate is still unproved.

CONCLUSIONS

In conclusion, According to our review and by considering COVID-19 as a new respiratory tract viral infection, this may prompt clinicians to use *nigella sativa*, natural honey, probiotics and paraprobiotics in the treatment of COVID-19.

Conflict of interest

The authors state that there are no conflicts of interest.

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