Prevention and treatment of upper respiratory diseases in the pandemic COVID-19 era

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In the pandemic coronavirus disease 2019 (COVID-19) era, the need to use preventive-curative treatments is compelling. A series of non-pharmacological compounds, including oligo-elements, vitamins, nutraceuticals, and bacteriotherapy, might affect the risk of COVID-19, both reinforcing the immune system and improving the inflammation resolution during respiratory infections. Non-pharmacological remedies are very popular and usually have no relevant side effects. Bacterial and natural products may potentiate the immune system against respiratory viruses. Moreover, these compounds also exert anti-inflammatory and antioxidant activity. Consequently, these non-chemical remedies could be prescribed to build up the immune defence and adequately treat the upper respiratory infection. In this way, natural compounds could be used to manage people in the pandemic COVID-19 era.

Background

Coronavirus disease 2019 (COVID-19) is a new emerging health problem with dramatic consequences. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first cases occurred in Wuhan (China) at the end of 2019. Then, the plague spread worldwide, and the World Health Organization (WHO) declared the pandemic on March 11, 2020 (1). This dramatic pandemic is continuously in progress, and there is a severe concern for a second wave. In this scenario, there is the awareness that no specific treatment nor a vaccine is currently available.

COVID-19 presents a broad clinical spectrum that ranges from asymptomatic disease to acute respiratory distress syndrome and multiorgan failure (2). COVID-19 is, therefore, a multifaceted, multiorgan, multi-system disease and affects every age.

From a pathophysiological perspective, the pathogenesis of severe COVID-19 entails both a hyper-inflammatory response and hyperstimulation of the immune system (cytokine storm), as widely pointed out (3). Several pharmacological treatments have been used, including antiviral drugs, anti-inflammatory drugs (corticosteroids and heparin), anti-cytokine biologics, and hyperimmune plasma. Numerous experimental trials have been performed or are ongoing, but definitive evidence still lacks the gold standard therapy.

On the other hand, preventive hygienic precautions, such as social distancing, facial mask, and handwashing, are undoubtedly essential for mitigating the infection's dissemination, but cannot be considered sufficient. In this regard, natural substances, such as non-chemical compounds, could be a reasonable way to prevent COVID-19, modulating the immune system, and resolving the inflammation associated with upper respiratory infections. The outcome could be to increase the defenses against infections. Moreover, non-pharmacological remedies have a consolidated

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efficacy combined with optimal tolerability and safety. These remedies include bacteriotherapy, nutraceuticals, and food supplements.

Bacteriotherapy

Recently, increasing attention has been paid to the concept of microbiota (4, 5). The concept that an infection changes the healthy composition of microbiota has long been well known (6, 7). Consistently, the healthy composition of bacteria in the upper airways could inhibit pathogens' growth (8). As a proof of concept, the recolonization with "interfering" bacteria could restore the physiological microbioma and prevent RRI (9). A possible mechanism is the capacity of some strains of α Streptococci of producing bacteriocin-like inhibitory substances (BLIS) able to contrast pathogens (10). Therefore, modulation of upper airways microbioma could represent an intriguing option (11). The term "bacteriotherapy" has been coined over 70 years ago (12). The first experiences were collected in the early '50s (13-15). Bacteriotherapy has been re-evaluated later using bacteria as probiotics throughout the maintenance or restoration of a physiological microbiome. The mechanism involves the interference and/or inhibition of pathogens from the production of antimicrobial proteins and immunomodulating mediators (12). In this regard, one strain, *Streptococcus salivarius* 24SMB, has been evaluated. *S salivarius* is a non-pathogenic species that colonize the oral cavity and is a primary BLIS (16). A study demonstrated that this strain had potent activity against *S pneumoniae*, was harmless to other *S salivarius* species, was non-pathogenic, and adhered to human larynx cells (17). A further study provided evidence that the topical administration of *S salivarius* by nasal spray colonized the nasopharynx (18). Therefore, these preliminary studies paved the way for a new approach based on the local administration of "friend" bacteria. In particular, the local bacteriotherapy approach re-colonize upper airways with healthy microbes and displace pathogens by bacterial interference (10).

Nutraceuticals

In COVID-19 patients, exaggerate inflammatory response, impaired innate and acquired immune activity, and oxidative stress are frequently detected. Oxidative stress and inflammation are closely associated as well as coagulative disorders are frequently observed in severe COVID-19. There are medical devices and food supplements claiming anti-inflammatory, antioxidant, and immunomodulatory activities. In this regard, we focus the attention on some substances, including lactoferrin, β-glucan, glycyrrhetic acid, vitamin C and D, and D-panthenol. All these natural components could exert synergistic effects providing a good effect in preventing respiratory infections and potentially for COVID-19.

Lactoferrin

Lactoferrin is a glycoprotein of human secretions that is part of the non-specific defensive system, such as the innate immunity (19). Lactoferrin exerts a relevant activity against microbial and viral infections and provides anti-inflammatory effects (20,21). Its anti-inflammatory activity depends on its ability to enter, through receptor-mediated endocytosis, inside host cells, and to translocate into the cell nucleus (22). Lactoferrin regulates, in fact, the pro-inflammatory gene expression at this level (23). Consequently, lactoferrin down-regulates the production of pro-inflammatory cytokines, reinforcing the acquired immune response as demonstrated in *in vitro* and *in vivo* studies and clinical trials (24-27). There is convincing evidence that lactoferrin exerts important antiviral activity against many viral families, including *Retroviridae*, *Papillomaviridae*, *Herpersviridae Adenoviridae*, *Pneumoviridae*, *Orthomixoviridae*, *Hepadnaviridae*, *Picornaviridae* (28). Lactoferrin antagonizes the viral entry into host cells through its competitive binding to the cell surface receptors (29). Moreover, lactoferrin prevents viral infections activating dendritic cells (30). Therefore, lactoferrin acts in the early phase of viral infections.

B-glucans

B-glucans are natural molecules that have highly conserved structures, which act as PAMPs (31). Glucans are polysaccharides exerting immunomodulatory activity, mainly concerning

cellular immunity. Macrophages are the principal target of glucans and monocytes, dendritic cells, and NK have receptors for them. Glucans modulate transcription factors and dampen the release of pro-inflammatory cytokines, mostly IL-6, IL-8, and TNF-α (32). Moreover, glucans promote a type 1 immune response increasing interferon production (33). Therefore, β-glucan plays a crucial role in enhancing the immune response against infections.

Glycyrrhetic acid

Glycyrrhetic acid (GA) is the most active glycyrrhizin component, a glycoside alkaloid present in *Glycyrrhiza glabra* roots (34). GA inhibits the HMGB1 chemotactic and mitogenic functions, without impeding DNA binding, which exerts important anti-inflammatory activity. GA is well tolerated, even at high concentrations (35).

Vitamin C

Vitamin C is an antioxidant; consequently, it is most evident under conditions characterized by elevated oxidative stress. A paradigmatic example is provided by the infections in which activated phagocytes release an abundant quantity of oxidizing substances, such as reactive oxygen species (36). Vitamin C is an efficient water-soluble antioxidant and may protect host cells against these agents' actions released by phagocytes. Moreover, vitamin C promotes interferon production (37). Therefore, vitamin C plays a relevant adjuvant activity during infections.

Vitamin D

Vitamin D (VD) is an essential hormone for humans as exerts pleiotropic effects, including anti-inflammatory activity (38). Throughout the body, many cells express the VD receptor (VDR) and the enzyme 1α-hydroxylase (39). A relationship between VD status and the incidence and the severity of RI in children has been found in many observational studies; mainly, the link between severe deficiency and susceptibility to RI is prototypically represented by the high respiratory morbidity in children with rickets (40). Low VD status (< 50 nmol/L) is an independent risk factor for treatment failure and delayed recovery from severe lower RI in children (41). VD supports the innate and adaptive immune response and plays a role in fighting pathogens, suggesting the need to guarantee an adequate status, particularly for patients with acute or chronic infections with profound VD deficiency. The benefit is notably higher in those receiving daily or weekly VD without additional bolus doses (42).

Panthenol

Panthenol (also called pantothenol) is the alcohol analog of pantothenic acid (vitamin B_5) and is a provitamin of B_5. In organisms, it is quickly oxidized to pantothenic acid. It is a viscous, transparent liquid at room temperature. Panthenol is used as a moisturizer to improve wound healing in pharmaceutical and cosmetic products (43). It improves hydration, reduces inflammation, and accelerates mucosal wounds' rate of healing (44). Panthenol readily penetrates the mucous membranes (including the intestinal mucosa), quickly oxidized to pantothenic acid. It is also used in the biosynthesis of coenzyme A, which controls a wide range of enzymatic reactions.

CONCLUSIONS

The pandemic COVID-19 era taught us that there is a compelling need to identify a potential preventive strategy to avoid infection and, if infected, minimize inflammatory consequence. In this regard, the use of non-chemical remedies should be welcome. There are several products, but the choice should be oriented toward compounds with adequate evidence. Lactoferrin is a natural component, so it is safe and well-tolerated at any age, mainly in children. In particular, lactoferrin is an essential physiologic immunomodulant in early life able to act on different targets, including the immune system, cellular replication, virus, bacteria, parasites, and fungi (Fig. 1). A new multi-component medical device contains other natural biological agents, including β-glucan, glycyrrhetic acid, vitamin C and D, and D-panthenol. All these substances have synergistic activity in preventing and fighting a respiratory infection (Fig. 2). In the absence of specific vaccines and medications, this new therapeutic strategy could

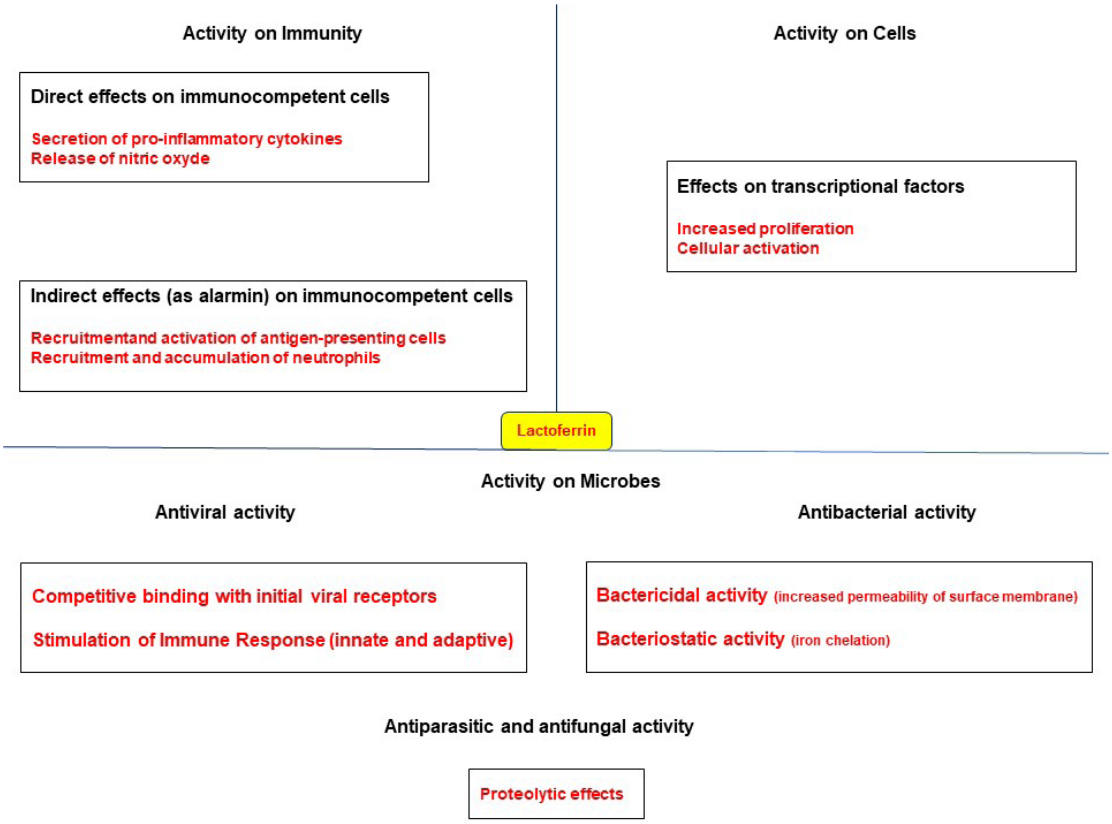

Fig. 1. *Mechanisms of action of Lactoferrin on immunity, cells, viruses, bacteria, and fungi*

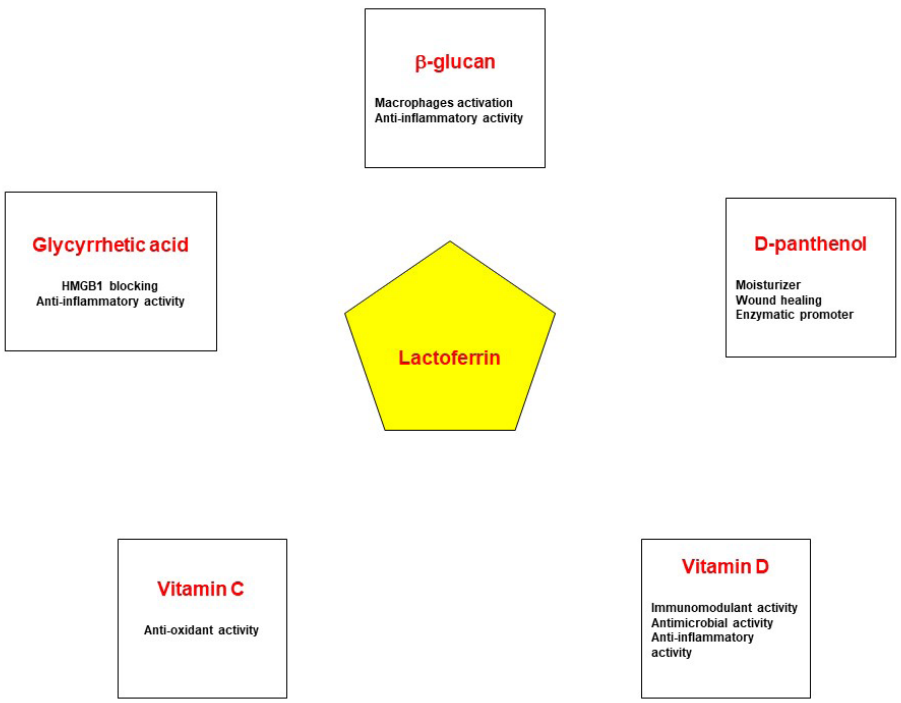

Fig. 2. *Synergic effects exerted by the components contained in a new medical device*

also be useful from an emotional point of view, as people are looking for valid preventive options. Of course, there is a need to provide adequate evidence to support this opportunity.

In conclusion, our opinion is that preventive bacteriotherapy and other natural substances, as well as early treatment of upper airway infection with anti-inflammatory and antioxidant compounds, could represent an appropriate strategy to potentially prevent COVID-19 in the general population and overall in at-risk subjects, mainly concerning children, elderly subjects, and people with fragility.

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