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Overview of available vitamin and supplement products used to improve immune system function

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ABSTRACT:

Introduction:

Questioning how we can boost our immunity during the infectious season often arises in the general practicioner's office. Patients report issues with recurring infections, affecting not only children but also adults, particularly those in professionally exposed groups such as teachers. Therefore, is it worthwhile to recommend over-the-counter (OTC) products available in pharmacies to patients, aiming to strengthen their immunity? This article

discusses the most commonly used supplements and immune-boosting preparations by patients and physicians, along with scientific evidence regarding their effectiveness.
Material and methods: The basis of the work were medical articles collected in the PubMed database. The research was conducted by analyzing key words such as: vitamin D3, immunity improvement, zinc, bacterial lysates, lactoferrin, fish oil, omega-3 fatty acids, *Echinacea purpurea*, *Spirulina maxima,* curcumin, probiotics, ginseng.
Results: In the pharmaceutical market, there are many supplements aimed at boosting the immune system. However, most of them lack sufficient scientific evidence regarding their effectiveness. The studies conducted so far are of low quality and limited in number. Further research is necessary to demonstrate the efficacy and safety of immune-boosting supplements.

Keywords: vitamin D3, immunity improvement, zinc, bacterial lysates, lactoferrin, fish oil, omega-3 fatty acids, *Echinacea purpurea*, *Spirulina maxima,* curcumin*,* probiotics, ginseng, antiviral, infections.

INTRODUCTION:

Numerous elements tied to our lifestyle affect the human body's immune system. These include factors like the duration of sleep, a well-rounded diet supplying essential vitamins and micronutrients, and consistent physical activity. Negative influences on immunity encompass exposure to tobacco smoke, ongoing stress, and irregular body weight, whether due to obesity or undernourishment. Scientific evidence also supports the positive effect of breastfeeding infants for the initial two years of life on their immune system.[1].

For many years, there has been a search for substances whose supplementation could strengthen human immunity, reduce the likelihood of falling ill after contact with a virus or bacterium, or at least shorten the duration of illness and the likelihood of a severe course.

Research on substances that can strengthen the immune system and potentially alleviate the effects of viral or bacterial infections is indeed a lengthy and complex undertaking. Researchers and health enthusiasts have explored various avenues, examining the potential of different supplements, dietary interventions, and lifestyle changes to improve the body's immune response.

One area of particular interest has been the impact of vitamins and minerals on supporting the immune system. For example, vitamin C, known for its antioxidant properties, has been studied for its potential ability to reduce the severity and duration of common illnesses.

Similarly, vitamin D has been implicated in immune regulation, and deficiencies in this vitamin are associated with an increased risk of infection.

Beyond vitamins, there is growing interest in the potential of probiotics for immune health. The gut microbiota plays a crucial role in the functioning of the immune system, and maintaining a healthy balance of gut bacteria may contribute to overall immune resilience.

Herbal supplements and traditional treatment methods have also been investigated for their immunomodulatory properties. Substances such as echinacea, spirulina, curcumin and ginseng have been studied for their potential to enhance immune responses. However, it's important to note that scientific evidence confirming the effectiveness of these substances may vary, and additional research is often needed to establish clear recommendations.

1. Vitamin D3

Vitamin D3 is a fat-soluble vitamin that plays several essential physiological roles. It is necessary for the absorption of calcium and phosphorus, crucial for maintaining healthy bones and teeth. Vitamin D3 also participates in the function of the immune system and exhibits anti-inflammatory effects. The immunomodulatory effects of vitamin D3 include the activation of immune cells such as T and B lymphocytes, macrophages, and dendritic cells, as well as the increased production of antimicrobial peptides and neutralizing antibodies. It is also responsible for inhibiting inflammatory cytokines.

Currently, a deficiency of vitamin D3 is widespread worldwide, with an estimated 40% of the European population suffering from its deficiency [2]. Vitamin D3 plays a significant role in protecting the body against pathogens. Studies indicate that maintaining a vitamin D3 concentration above 50 ng/ml is associated with a reduction in the risk of infections [3]. It has been demonstrated that vitamin D3 has proven supportive effects in infections, particularly in individuals with a deficiency.

Should everyone, then, have their vitamin D3 levels measured? Guidelines for supplementation suggest that it should be done in patients at risk, including those who are obese, have reduced sun exposure, are dark-skinned, have rickets, osteomalacia, low-energy fractures, osteoporosis, chronic kidney and liver failure, autoimmune diseases, use elimination diets, or are chronically hospitalized. In these patients, the vitamin D3 dose is adjusted based on the level of deficiency. For patients outside of these groups, the decision to supplement with vitamin D3 depends on the patient's age and the time of year [4].

Studies indicate that people deficient in vitamin D3 are more likely to experience conditions such as tuberculosis, influenza type A, common cold, upper respiratory tract infections, lower urinary tract infections, bacterial vaginosis in pregnant women, gum diseases, jaw osteonecrosis, various fungal infections, and infections with Sars-CoV-2, Coxsackie A, and B [3].

Severe deficiencies in vitamin D3 were identified among patients who died from Covid-19 between 2020 and 2021. The deficiency of this vitamin was shown to be linked to a severe progression of Covid-19 [2]. While there is no conclusive evidence that vitamin D3 prevents viral infections, including Covid-19, there is proof that maintaining an adequate level of vitamin D3 reduces disease symptoms and lowers the occurrence of complications, hospitalizations, and fatalities related to the illness [3].

2. Bacterial lysates

Bacterial lysates, also known as oral polyvalent vaccines from bacterial sources, consist of a blend of bacterial antigens acquired through the lysis of bacteria commonly responsible for respiratory tract infections [1].

In a study conducted in 2018, it was affirmed that bacterial lysates boost immune resistance, decrease the frequency of recurrent respiratory tract infections in both adults and children, alleviate the severity of respiratory symptoms, shorten the duration of infection-induced fever, and reduce the number of infections necessitating antibiotic treatment. Nonetheless, it's important to note that for specific acute bacterial respiratory infections, bacterial lysates should not be seen as a substitute for proper antibiotic therapy [5].

Several bacterial lysate products are available in the Polish market. According to the 2019 opinion of the European Medicines Agency (EMA), bacterial lysates should be exclusively used to prevent recurring respiratory infections, with the exception of pneumonia. This decision followed a review that identified a lack of robust data supporting the efficacy of these products in treating existing respiratory infections or preventing pneumonia. Therefore,

they should not be employed for these purposes. However, given the favorable safety and tolerance profile of bacterial lysates, along with some evidence of effectiveness, the EMA recommended the continued use of these medications for infection prevention. In its statement, the EMA also stressed the necessity for further randomized clinical trials to better evaluate the efficacy and safety of bacterial lysates [6].

A 2020 study underscores the importance of developing more standardized protocols for preparing bacterial antigens. This is because existing literature either lacks detailed bacterial lysis procedures or keeps these procedures inaccessible to the research community. The effectiveness of bacterial lysates is significantly influenced by the chosen inactivation method, warranting in-depth exploration. The absence of standardized protocols results in variable extract efficacy across laboratories, posing a challenge to reproducibility. Consequently, this variability may lead to misleading assessments of the effects of individual bacterial lysate preparations. Establishing standard production protocols would be a beneficial measure in addressing current challenges related to comparing the immunological and clinical effects of bacterial lysates and their use in immunotherapy for preventing and treating respiratory infections [7].

The challenge associated with bacterial lysate use lies in the insufficient number of studies proving their efficacy, compounded by the fact that the majority of respiratory infections are caused by viruses rather than bacteria.

3. Lactoferrin

Lactoferrin, a glycoprotein present in mucous membrane secretions, boasts diverse functions, including immunomodulation and anti-inflammatory properties. Numerous studies affirm its potent efficacy against various bacteria and viruses, suggesting it may serve as a potential inhibitor for viruses like SARS-CoV-2 [8].

The mechanism of lactoferrin is well-documented; it binds to iron ions, rendering iron inaccessible to bacteria and inhibiting their growth. Notably, studies indicate that, due to distinct digestion processes, lactoferrin provides greater benefits when supplemented in infants compared to adults.

In the context of the COVID-19 pandemic, a randomized, placebo-controlled, multicenter clinical trial explored the impact of lactoferrin on the progression of the infection. Results revealed no significant influence of lactoferrin on altering the clinical course or inflammatory indicators in hospitalized adults with moderate to severe COVID-19 when used as an additional treatment [9].

However, the overall research on lactoferrin supplementation in humans presents mixed findings. To position lactoferrin as a supplementary or alternative treatment for various respiratory conditions, additional evidence and well-conducted clinical trials are imperative to establish its efficacy in human contexts [12].

Lactoferrin administration displays promising efficacy in lowering the risk of respiratory infections. Current evidence also supports the enrichment of infant formula with lactoferrin. While lactoferrin may play a beneficial role in symptom management and recovery for individuals with respiratory infections and hold potential as an adjunct in COVID-19, robust evidence from extensive, well-designed studies is needed to solidify these claims [10].

4. Zinc

Zinc, a vital trace element, plays a crucial role in growth, development, and maintaining immune function. It's present in almost 10% of the human proteome, influencing numerous enzymes and transcription factors across all organs and cell types. Despite its importance, zinc

deficiency is widespread, affecting around a quarter of people in developing nations and specific groups in developed countries due to various lifestyle, age-related, and disease-related factors. This deficiency significantly impacts antiviral immunity, making zinc-deficient populations more susceptible to viral infections like HIV or hepatitis C.
Over the last 50 years, substantial evidence has emerged demonstrating zinc's effectiveness against various viruses through multiple mechanisms. The use of zinc to treat viral infections like herpes simplex virus and the common cold has emerged from these findings.[11]
The findings from examined research suggest that zinc, along with certain zinc-related proteins, plays a role in defending against viruses and regulating the immune system in the respiratory tract. It appears that zinc could lower the amount of virus after getting the flu. It might also lessen the impact of RSV in the lungs and shorten the duration of symptoms from viral pneumonia. There's a possibility that zinc could boost the effectiveness of hydroxychloroquine in reducing the death rate among COVID-19 patients.[12]
Research consistently indicates that severely ill patients often have reduced zinc levels in their blood, and their recovery from critical conditions is linked to restoring these levels. There's strong biological reasoning supporting the potential benefits of providing high-dose zinc supplements to critically ill patients, considering the crucial role zinc plays in supporting the immune system.[13]
Furthermore, oral zinc supplementation in children living in rural areas significantly reduced the occurrence of both diarrhea and acute lower respiratory infections.[14]
In places with a high risk of zinc deficiency, the advantages of using zinc supplements to prevent problems might be greater than any possible negative impacts.[15]

5. Omega-3 fatty acids

Of all the fatty acids, omega-3 polyunsaturated fatty acids (PUFA) exhibit the strongest immune-modifying effects. Specifically, within the omega-3 PUFA category, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived from fish oil are more biologically powerful compared to alpha-linolenic acid (ALA).[16]
Omega-3 fatty acids, which consist of eicosapentaenoic and docosahexaenoic acids, are polyunsaturated fats recognized for their positive impact on immunity and reducing inflammation. Notably, they demonstrate antiviral effects by slowing down influenza virus replication. According to the European Society for Parenteral and Enteral Nutrition, using omega-3 fatty acids might enhance oxygen levels in COVID-19 patients, yet concrete evidence supporting this is currently lacking.[17]
Fresh oils with a greater amount of DHA relative to EPA, like fractionated and concentrated fish oil, tuna oil, calamari oil, and microalgae oil, are becoming more prevalent in the market. Additionally, there are expectations for other oils, including those extracted from genetically modified oilseed crops, to soon become available.
Presently available information strongly supports DHA as a valuable active component that benefits heart health, cardiovascular function, and brain performance. It exhibits diverse effects, occasionally complementing those of EPA. Moreover, DHA has shown promise in decelerating cognitive decline, although its potential impact on depression disorders remains uncertain.[18]
Long-chain omega-3 polyunsaturated fatty acids could potentially bring about beneficial outcomes in immune response, inflammation, oxidative stress, and psychoneuroimmunity during various phases of SARS-CoV-2 infection. Particularly, EPA among the omega-3 PUFAs has demonstrated effects in addressing mood and neurocognitive disorders by reducing pro-inflammatory cytokines. Additionally, omega-3 PUFAs and their byproducts, which include specialized mediators, expedite the resolution of persistent inflammation and

the restoration of tissue balance, offering a promising approach for addressing Long COVID.[19]
Upon reviewing many studies, it might not be conclusively viable to recommend altering the intake of omega-3 LCPUFA through diet or supplementing omega-3 LCPUFA specifically to treat or prevent asthma in clinical settings. A definitive conclusion cannot be drawn supporting the positive impact of dietary changes or omega-3 supplementation in preventing or altering asthma in children. It's evident that further research is necessary in this area, especially focusing on the dietary influence during early life and the aspect of individual susceptibility.[20]
Moreover, DHA has been found to have a potential role in inhibiting rhinovirus-induced airway inflammation, while rhinovirus infections in childhood, as has been widely demonstrated, may lead to the development of bronchial asthma in the future.[21]

6. Echinacea purpurea

Preparations derived from Echinacea purpurea are commonly selected herbal supplements known for their immune-supporting properties in the market. As per a 2020 NBJ report, Echinacea represented 4.3% of the $3.4 billion total revenue from the sale of supplements targeting colds, flu, and immune enhancement in 2019. Sales are projected to grow exponentially in the years following 2020 [24].
These Echinacea purpurea preparations contain a distinctive mix of various phytochemicals, such as phenols, alkaloids, alkamides, polysaccharides, terpenoids, vitamins, and fructans. These elements activate or regulate the immune system through direct or indirect mechanisms, influencing T cells, macrophages, lymphocytes, and cytokines. Echinacea may exhibit effects like anti-inflammatory, immunomodulatory, antiviral, and antibacterial properties [22].
Products like Esberitox, commonly used in Poland, made from Echinacea purpurea, are effective in preventing and aiding the treatment of upper respiratory tract infections in adults. A study suggests that Echinacea purpurea supplementation reduces the risk of catching a cold by 58% and shortens its duration by 1.4 days. In children, Echinacea purpurea might assist in preventing colds when used during the flu season. However, it doesn't reduce the length or severity of symptoms during infections in children [23].
Concerns arise about the quality of conducted studies. Some research indicates that the impact of Echinacea purpurea supplementation is marginally higher or comparable to a placebo. Generally, it is safe to use, with common side effects limited to mild gastrointestinal symptoms or rashes [24].
Studies on Echinacea purpurea supplementation in Covid-19 infections have been conducted, but as of now, there is insufficient data confirming its effectiveness. Future research should explore the potential use of Echinacea purpurea as a preventive measure or therapeutic addition in COVID-19 infections and as an immune booster in individuals at risk or with existing health conditions [22].
In conclusion, at present, there is a lack of well-conducted studies indicating a substantial impact of Echinacea purpurea preparations on the progression of infections in both children and adults.

7. *Spirulina maxima*

For years, researchers have been captivated by nutraceuticals due to their numerous properties, particularly their potential in managing viral infections.

Spirulina, also known as Arthrospira platensis, is a type of Cyanobacterium belonging to the Cyanophyceae class. It boasts an extensive array of properties and has been utilized for more than four centuries. [25]
Spirulina reduces the replication of viruses and blocks their replication and is completely non-toxic to human cells. Spirulina extract has been shown to inhibit viral cell penetration and replication of herpes simplex virus type 1 (HSV-1) in vivo. The extract has been shown to inhibit viral protein synthesis without suppressing host cell function. The antiviral effect is attributed to a sulfated polysaccharide called "Calcium Spirulate", which has been shown to inhibit the replication of many enveloped viruses. Calcium spirulan (Ca-Sp) has currently been shown to have activity against human cytomegalovirus, measles virus, mumps virus, influenza A virus, human immunodeficiency virus (HIV-1), as well as HSV-1.[26]
In addition, recent studies have shown that spirulina extract also inhibits the replication of the respiratory syncytial virus (RSV) and prevents the virus from entering cells. [27]

8. Curcumin

Curcumin, a natural polyphenolic compound extracted from the rhizomes of the turmeric plant, also known as Indian saffron, belongs to the ginger family. This plant exhibits a broad spectrum of anti-inflammatory, antibacterial, antiviral, and antifungal properties.
The anti-inflammatory properties of curcumin are a result of reducing the activity of cyclooxygenase-2 (COX-2), lipoxygenase (LOX), inflammasome, and inducible nitric oxide synthase (iNOS). Additionally, curcumin hinders the production of pro-inflammatory cytokines and chemokines, including IL-2, IL-6, IL-8, IL-12, TNF-α, macrophage inhibitory protein (MIP), and monocyte chemoattractant protein-1 (MCP-1). [28]
The first indication of curcumin's antiviral properties surfaced in the 1990s when it was discovered to inhibit the human immunodeficiency virus (HIV) viral protease in vitro [29].
One study found that administering curcumin nanoparticles intravaginally (but not orally or intraperitoneally) to the genital tract of mice could alleviate tissue inflammation. This approach also reduced the production of pro-inflammatory mediators, including TNF-α, IL-6, and MCP-1. The potential outcome of this intervention is a reduction in the severity of HSV-2 infection and a lowered risk of HIV transmission. In a different study, it was found that curcumin has the potential to hinder and/or regulate the proliferation of viruses in the female reproductive tract [28].
Curcumin has been also recommended as a dietary supplement to prevent mucosal damage associated with Helicobacter pylori (H. pylori) infection. [28]
While curcumin shows potential as an antimicrobial substance, it is hindered by several limitations. Curcumin is nearly insoluble in water, resulting in low in vivo bioavailability. Only a minimal amount, as low as 1%, of administered curcumin is absorbed by the body, and it remains challenging to detect in target tissues. [29]
Clinical trials for treating various disease states or pathological disorders with curcumin in humans are limited [28].

9. Probiotics

In clinical practice, probiotics containing bacteria from the genera Lactobacillus, Bifidobacterium, and Bacillus, as well as the yeast Saccharomyces boulardii, are most commonly used. They exhibit immune-supporting properties by competing with pathogens for nutrients and adhesion molecules.

Substantial evidence suggests that immune cells in the intestinal tract engage with probiotics consumed through diet, leading to improved immune balance and functionality. While probiotics have been studied extensively, only a limited number of investigations have delved into the molecular mechanisms underlying the immunomodulatory effects of these bacteria and their interactions with the host's immune cells. Probiotics, when ingested, specifically impact the activation and modulation of both innate and acquired immune responses within the intestines. This stimulation results in the production of various cytokines and chemokines by cells such as dendritic cells, lymphocytes, macrophages, mast cells, granulocytes, intestinal epithelial cells, and IgA-producing cells, followed by the secretion of IgA. Consequently, probiotics can enhance the host's immune system, offering significant benefits in preventing or managing diseases associated with the immune or inflammatory systems, including inflammation, diarrhea, pathogenic infections, infant colic, and certain types of tumors. Despite some progress, the detailed mechanisms of interaction between ingested probiotics and immune cells in the gut remain incompletely understood. Therefore, further preclinical and clinical research is imperative to clarify these mechanisms [30].

Research on adults indicates that the use of probiotics is linked to a decrease in the number of adults facing upper respiratory tract infections, the rate of occurrence of acute upper respiratory tract infections, and the average duration of such infections. However, there is no evidence suggesting that probiotics contribute to reducing the number of patients ultimately requiring antibiotic treatment [31].

Throughout the COVID-19 pandemic, researchers explored the potential therapeutic benefits of using probiotics as supplementary treatment for COVID infections. Although some small clinical studies suggested an improvement in symptoms related to COVID-19, their direct effectiveness in addressing COVID-19 symptoms and outcomes like viral clearance or hospitalization duration was not consistently validated [32].

As our comprehension of the immune system and the interplay between probiotics and the immune system advances, it is anticipated that probiotics will assume a more significant role as supplementary therapies against viral infectious diseases [32].

10. Ginseng

Ginseng, referred to as "man-root," is a gradually maturing herbal root that has been employed in traditional Chinese medicine (TCM) for over 3000 years. [33]

Several research studies highlight the capacity of ginseng to regulate the immune system, potentially serving as a preventive measure against various diseases. While the human immune system consists of diverse cell types, numerous studies propose that ginseng or its derivatives can exert control or stimulation on each immune cell type. Preliminary assessments of ginseng's potential effectiveness against viruses, bacteria, and other microorganisms indicate its potential as a valuable pharmaceutical resource, especially with the availability of higher-quality evidence. [34]

Potential mechanisms underlying the antiviral effects of ginseng include enhancements in both systemic and mucosa-specific antibody responses, inhibition of serum hemagglutinin, promotion of lymphocyte proliferation, improvement in cell survival rates, and facilitation of viral clearance in the lungs. Additionally, ginseng diminishes the expression of proinflammatory cytokines (such as IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-6, IL-8) and chemokines produced by airway epithelial cells and macrophages, thereby preventing weight loss. In cases of bacterial infections, ginseng functions by mitigating inflammatory cytokine production, increasing survival rates, and activating phagocytes and natural killer cells. Furthermore, ginseng inhibits biofilm formation and induces the dispersion and dissolution of mature biofilms. Clinical trials consistently indicate that ginseng, administered at various

dosages, represents a secure and effective approach for seasonal prophylaxis, alleviating symptoms, and reducing the risk and duration of colds and flu. [35]

SUMMARY AND CONCLUSIONS:

Despite the widespread popularity of immune-boosting supplements, a considerable portion of them lacks robust scientific backing. The studies conducted thus far often suffer from methodological limitations, including small sample sizes, short durations, and a lack of rigorous control groups. As a result, the reliability and generalizability of these findings are questionable.

One of the challenges in assessing the effectiveness of immune-boosting supplements is the diversity of ingredients and formulations available in the market. Each product may contain a unique combination of vitamins, minerals, herbs, or other compounds, making it challenging to draw overarching conclusions about the entire category. This diversity further emphasizes the need for targeted research on individual components to unravel their specific impact on the immune system.

Moreover, the current body of evidence often falls short in addressing long-term effects and potential side effects associated with regular consumption of these supplements. Safety concerns are paramount, particularly when considering that individuals may self-prescribe or combine various products without proper medical guidance.

To address these gaps in knowledge, there is a pressing need for well-designed, large-scale clinical trials that adhere to rigorous research standards. These studies should not only investigate the efficacy of immune-boosting supplements but also delve into the nuances of their mechanisms of action, optimal dosages, and potential interactions with other medications. The scientific community, healthcare professionals, and regulatory bodies must collaborate to establish a robust foundation for evidence-based recommendations regarding immune-boosting supplements. Until such high-quality research becomes available, consumers are encouraged to approach these products with a healthy dose of skepticism and consult with healthcare professionals before incorporating them into their wellness routines. In the ever-evolving landscape of healthcare, fostering a culture of critical inquiry and evidence-based decision-making is essential for promoting the well-being of individuals seeking to fortify their immune systems.

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