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Efficacy of traditional herbal formulas on human immunity

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Abstract. – In the present study, we reviewed the efficacy of traditional herbal formulas on human immunity. A literature survey was performed in PubMed, UpToDate, Proquest Central Databases of Kırıkkale University, Google and Google Scholar databases from the internet. Search key words were "immune", "immune system", "herbal", "*Pelargonium Sidoides*", "*Echinacea Purpurea*", "*Sambucus Nigra*", "Beta Glucan", "Vitamin C", "Zinc". The immune system is a natural self-defense mechanism made up of cells that assist the body in distinguishing between self and non-self-molecules. All immune system components must be regularly modified in order to keep the body defenses up against the ever-evolving microbes that are constantly looking for new ways to attack the host. A Chinese herbal formulation is a combination of several herbs. The practitioner begins with one or two major substances that are intended to treat the ailment. The reproducibility of the efficacy of herbal medicines is dependent on the consistency of the quality of each unique raw herb. *Pelargonium Sidoides*, Echinacea Purpurea, Sambucus Nigra, Beta Glucan, Vitamin C, and Zinc are some herbal treatments utilized for their benefits on human immunity. Herbal remedies are undoubtedly valuable in boosting impaired immune function, particularly where damage has occurred due to malnutrition, chronic disease or previous infections. At present, however, an invincible immune system remains firmly in the realm of fantasy.

Key Words:
Immunity, *Herbal remedies, Pelargonium Sidoides, Echinacea Purpurea, Sambucus Nigra*, Beta Glucan, Vitamin C, Zinc.

Introduction

Herbal therapy, acupuncture, massage, and food therapy are all forms of traditional Chinese medicine (TCM). These procedures originated in China and have been used as a component of mainstream medical care in East Asia for centuries. TCM is also emerging as a complementary and alternative medicine (CAM) in Western healthcare[1].

Asthma, atopic dermatitis (AD), and food allergies have all seen dramatic increases in frequency in developed nations over the past few decades. In children, atopic diseases pose a serious threat to public health. Asthma and Alzheimer's disease are typically treated with conventional drugs like glucocorticoids[1]. The success of these treatments is not high in every patient, especially in the young ones. Furthermore, only emergency measures can alleviate the symptoms of a food allergy attack; there is currently no cure. Because of these and other concerns, many patients and their families are turning to CAM therapies[1].

Methods

A literature survey was performed in PubMed, UpToDate, Proquest Central databases of Kırıkkale University and Google and Google Scholar databases from the internet. Search key words are "immune", "immune system", "herbal", "*Pelargonium Sidoides*", "*Echinacea Purpurea*", "*Sambucus Nigra*", "Beta Glucan", "Vitamin C", "Zinc".

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The Immune System: an Overview

The immune system is a natural self-defense mechanism made up of cells that assist the body in distinguishing between self- and non-self-molecules. Different immune cell pathways assist the body discriminate its own healthy cells from disease-causing organisms such as bacteria, viruses, fungus, parasites, malignant cells, and many more[2].

All immune system components must be regularly modified in order to keep the body's defenses up against the ever-evolving microbes that are constantly looking for new ways to attack the host. This constantly changing system occasionally reacts against the body's own cells, misidentifying them as foreign, resulting in the death of healthy tissue and the development of autoimmune illnesses and malignancies.

The immune system has several stages of resistance against invading microorganisms. It is made up of physical barriers, innate immunity systems, and adaptive immunity processes. The physical barrier can be mechanical, chemical, or biological, and it can be found at several locations throughout the body, including the skin, secretions in the respiratory system, and flora in the gastrointestinal or genitourinary tract. Within the body, cells with innate and adaptive immunity can be found in a variety of locations, including the blood, lymphatic system (lymph, lymphoid nodules, and lymphoid organs), epithelium, and connective tissues[3].

Antigens

Molecules that are identified and activate immune system cells are called antigens. Both individual cellular components (proteins, polysaccharides, or nucleoproteins), and entire cells (tumor cells, or organisms containing genetic material, such as bacteria, viruses, fungi, parasites), or agents carrying nucleic acids or lipids, fall under this category[2].

There are two ways in which the adaptive immune system can respond to antigen: cellular or humoral. Lymphocytes play a crucial role in the cellular response, while plasma cells produce antibodies in the humoral response. The immune system recognizes specific regions of an antigen called epitopes, and these regions dictate whether the cellular or humoral immune response is mounted against the antigen. A linear amino acid sequence or an antigenic tertiary structure are both examples of epitopes[2].

Immunoglobulin

Immunoglobulins (Igs), which are sometimes referred to as "antibodies", are glycoprotein molecules made by B lymphocytes and plasma cells in response to an immunogen or following detection of certain epitopes on the antigen. Antibodies target individual antigens through specific binding. Humoral immunity relies heavily on Ig. The pre-B lymphocyte is the progenitor of all B-lymphocytes and the first cell in the body to make Ig. Daily Ig production by an adult individual is about 2-3 grams[2].

Antibodies are proteins that can be found in a variety of different locations in the body, including on the surface of lymphocytes as a component of the cell membrane protein, in the bloodstream, or as a gland secretion. The Ig molecule is a polypeptide heterodimer made up of four identical chains: two light chains and two heavy chains linked together *via* disulfide bonds[1].

The Ig family of proteins includes not only antibodies, but also the five isotypes (G, A, M, E, and D) and the subclasses G and A within each isotype. The properties of the antibody's Ig heavy chain serve as a dividing line between the groups. There are V (variable) regions and C (constant) regions in every chain. The antibody binding portion of the molecule to the various antigens consists of the variable region, which varies greatly amongst antibody molecules and consists of around 110 amino acids. Neutrophils, eosinophils, macrophages, dendritic cells, B cells, and NK cells all have Fc receptors that the constant area at the carboxyl-terminal end of the heavy chain, called the Fc region, binds to. The Fc region also plays a role in complement activation[1].

When antibodies bind to their target antigens, the antigens agglutinate and precipitate, rendering themselves ineffective. Covering the antigen's surface with the Fc region of the antibody stimulates the destruction of antigen by cells including macrophages, neutrophils, and eosinophils; this process is known as "opsonization[1]".

Strong Ties

For the Ig classes G, A, M, E, and D, the corresponding heavy chains are denoted by corresponding Greek letters (i.e., γ, α, μ, ε, δ). There are four distinct forms of human IgG, designated by the numbers 1, 2, 3, and 4. IgG1 has C1 as its heavy chain, for instance. There are just three CH domains in the constant (C) region of IgG, IgA, and IgD. The C sections of IgM and IgE have 4 CH domains[1] each.

κ and λ light chains can be distinguished by their C-terminal regions. Chromosome 2 encodes for κ, while chromosome 22 does the same for λ. It is impossible for an Ig molecule to have both the κ or λ (60% and 40%). It is impossible for a single B lymphocyte to generate both the κ or λ chains[1].

Regions that Vary

Antibody variety is due to complementarity determining regions (CDRs) of around 10 amino acids, which are located in the variable sections VL and VH and form the antigen-binding sites. Each V region has three complementary variable regions (CDRs), with CDR3 being the most variable and often making the most extensive contact with the antigen[1].

Continual Spaces

Continual Spaces the Ig molecule's C-termini are where CH and CL are found. Only CH binds to Fc receptors and complement to mediate effector activities[4].

Immune System Cells

Lymphocytes

Lymphocytes can be broken down even further into T cells, B cells, and NK cells. Lymphocyte subsets T and B can only recognize a certain antigen. The receptors found on the surface of each cell give rise to functional differences in their generation and maturation. The B-lymphocytes and natural killer cells both originate in the bone marrow before dispersing to other lymphoid tissues and organs. However, after leaving the bone marrow, T lymphocytes travel to the thymus gland, where they undergo a second round of selective maturation.

Lymphoid tissue contains these cells as well as many others that constantly circulate throughout the body. T cells predominate in the thymus, followed by the blood, the lymph nodes, and finally the spleen, while B lymphocytes predominate in the bone marrow, followed by the spleen, the lymph nodes, and finally the blood. The thymus gland does not contain any B lymphocytes.

When activated, B cells multiply rapidly and secrete antibodies that target the triggering antigen. In some cases, antigen is first delivered to T cells, which subsequently secrete cytokines that excite B lymphocytes. It causes the body to react by making antibodies to fight off the antigen. In addition, during repeated exposure, some B lymphocytes are transformed into memory cells that generate a fast response to the same antigen[2].

However, T cells can only recognize antigens presented to them coupled to the major histocompatibility complex (MHC), and they too are triggered by receptors on their surface. There are two types of T lymphocytes, the cytotoxic and the helper T cells. T cells that are able to bind to MHC class II molecules are known as helper T cells or CD4+ T cells. When activated, they release a plethora of cytokines which induce the differentiation of B cells into plasma cells, that in turn promotes the manufacture of more antibodies[2].

The inflammatory response against the given antigen is heavily influenced by cytotoxic T cells and macrophages. CD8+ T cells, also known as MHC Class I restricted T cells, are the cytotoxic T cells. The first way they kill cells is by latching to them and releasing proteins, called perforins, into the cells, which poke holes in the target cell membranes and cause the cells to lyse. Second, they cause apoptosis, which is a form of planned cell death[2].

Innate immune system cells

In the same way that B and T lymphocytes contain antigen-recognizing receptors on their surface, natural killer cells have them too. They initiate a direct, asymptomatic assault on aberrant or foreign cells, such as cancer and virus-infected cells[2].

Cells that display antigens

B lymphocytes, macrophages, and dendritic cells (also known as Langerhans cells in the mucosa and epidermis) are all examples of antigen-presenting cells. Helper T cells (CD4+) are presented with peptides bound to class II major histocompatibility complex (MHC) molecules on the surface of these cells.

How Does the Immune System Work?

The antigen presenting cell and major histocompatibility complex pathways

Human leukocyte antigens (HLA) are a subset of major histocompatibility complex (MHC) molecules that are encoded on the MHC locus[2].

Serological tests were used to detect the presence of MHC molecules at the outset. HLA-A, -B, and -C were the initial MHC molecules discovered. The mixed lymphocyte response assay[2] was used to determine the presence of HLA-DR, DQ, and DP.

The following are characteristics shared by MHC molecules[2]:

- One binding site exists on each MHC molecule.
- Cell membranes are where MHC molecules are anchored.
- MHC Class I and II restricted interactions with T lymphocytes necessitate physical touch.
- Co-dominant expression of MHC molecules.
- Cell surfaces express parental MHC molecules

Transmission of antigens for MHC class I

- The endoplasmic reticulum is still the safe haven for newly generated MHC class I polypeptides.
- The proteasome degrades organisms that reach the cytoplasm into antigenic peptides.
  The proteasome is a multi-subunit proteinase, and transporter associated with antigen processing (TAP) proteins bring antigenic peptides to the endoplasmic reticulum to be processed. Newly generated MHC class I polypeptides are primed with antigenic peptides. The antigenic peptide and MHC class I are taken to the cell surface.
- Antigenic peptide[2] is necessary for stable MHC class I expression.

The processing of MHC class II antigens

Phagosomes in the cytosol collect and store antigens taken in from the extracellular environment *via* Fc or complement receptors. Phagosomes combine with lysosomes to form a single structure. The bacterium is digested into antigenic peptides[2] in the resultant phagolysosome.

Cytokines

These include soluble protein molecules (such as IFN-, IL-4, TGF-beta, IL-13, IL-5), which are released by a wide variety of cells in the body (not just immune system cells like lymphocytes, macrophages, or leukocytes)[2].

To stimulate the immune system, these cytokines have a role in the control of a wide variety of other processes, including growth, development, and the mediation of the inflammatory response. When cytokines have an effect on the cells from which they were secreted, this is called an autocrine effect; when they have an effect on neighboring cells, this is called a paracrine effect; and when they are secreted into the circulation and have an effect on a target organ far from their secreting cells, this is called an endocrine effect[2].

Immunity's Physical Defenses

Some examples of such physical obstacles are as follows[2]:

- Skin
- Nails

Barriers in the mucosa

- Fluids produced by the lungs, stomach, and urine systems
- Cilia in the nose

Natural defenses

The components of innate immunity include antimicrobial peptides, pattern recognition receptors, cells, complement components, and a variety of cytokines. It is the first line of defense, but it does not make any long-term memories of the antigens that attacked you.

Innate immunity

T lymphocytes are mostly involved in the cellular response while B lymphocytes are primarily involved in the humoral response during adaptive immunity. After being activated, T lymphocytes secrete a plethora of cytokines that instruct macrophages and other cells to eliminate the presenting antigen. Antigens are destroyed when T cells secrete cytokines that induce B lymphocytes to make antibodies against them. Memory T cells and memory B cells are formed by the immune system following the initial exposure in adaptive immunity, allowing for a more rapid and targeted immune response during repeated encounters with the same pathogen or antigen[2].

Immunoglobulin production by B cells, which originate in bone marrow and mature there. Linear epitopes, key ligands, markers, and connections (Fc receptors, CD19, CD20, CD21, and MHC II) are all things they can identify.

T lymphocytes are matured B lymphocytes that have their origins in bone marrow. The epitopes they detect are conformational.

There are three possible subtypes of T lymphocytes: CD4+ helper T cells, CD8+ cytotoxic T cells, and Tregs.

T cells can be further subdivided into effector T lymphocytes and memory T lymphocytes after activation. A second stimulus, or co-stimulation, is needed for activation. Antigen-presenting cells are cells in which the costimulatory chemicals can be found. Their receptors can be found on T cells. Without costimulation, the T lymphocyte response would not occur. An energized (or non-responsive) T cell is one that detects the antigen but does not receive the costimulatory signal.

Inducing negative modulation of the immune response[2] is one possible effect of costimulators.

Herbal Remedies for Immune Function

TCM treats the whole person, not just the symptoms or the affected organ. Rather, it also emphasizes homeostasis of organ systems, interactions with the environment, and the yin-yang balance (two opposed, but complimentary forces) of the body and mind[5]. There is no direct equivalent in Western medicine for the ideas and terms of traditional Chinese medicine[1].

Every patient receives individualized care. A Chinese herbal formulation, for instance, is a combination of numerous herbs. To treat an ailment, the doctor first uses one or two primary substances. The specific yin-yang conditions of the patient determine which additional substances are included as a catalyst to increase the efficacy of the other components or as an antidote to counteract the negative effects of the other ingredients. As a result, the formulation employed to treat a given condition differs from patient to patient and even within a single patient according to their evolving requirements[1].

Randomized clinical trials have not been conducted on TCM. For instance, sham acupuncture is notoriously tricky to carry off. Herbal formulations are not always standardized in terms of their contents, and even when they are, the quality and pharmacologic activity of the different herbs within the formulation can vary.

To fill up some of the blanks in our understanding of CAM, the National Institutes of Health's National Center for Complementary and Integrative Health (NCCIH) funds both clinical and basic research. To further improve the quality of Chinese herbal medicine, the National Committee of Acupuncture and Oriental Medicine also offers a diploma in Chinese Herbology.

TCM relies heavily on the use of Chinese herbal remedies, which are widely given in China both on their own and in tandem with Western treatment. In the United States, the Food and Drug Administration (FDA) classifies Chinese herbs as dietary supplements. Therefore, there is no requirement for proof of efficacy, safety, or quality, and no obligation to disclose post-marketing adverse events[1].

The FDA recommendations[6] for the study of botanical medicine products, such as complicated formulae containing multiple plants, with an emphasis on efficacy, safety, and consistency. That is why it makes sense to look into traditional Chinese medicine supplements as potential new plant medicines. The Chemical, Manufacturing, and Control (CMC) Data requirement for new botanical drugs[6] is one of the main variations between the standards for researching synthetic and botanical medications set by the US Food and Drug Administration. Raw herb, extract, and finished product quality and safety information are all required for botanical medicines[1].

According to TCM, allergic sickness develops when the balance between the body's many organs and their environments and diets is disturbed, specifically concerning the lungs, skin, and digestive tract. There is much evidence[7,8] in TCM literature linking asthma, allergic rhinitis, and AD. Even though they have not been extensively researched[7,8], numerous widely used formulations exist for these conditions.

High-performance liquid chromatography (HPLC) fingerprinting of the molecular components is used to standardize the quality, potency, and consistency of formulations. Liquid chromatography combined with mass spectrometry[1] is also used to identify chemical markers.

The reproducibility of herbal therapy efficacy depends on the uniformity of the raw herbs used. According to the Pharmacopoeia of the People's Republic of China[7], factors that affect quality include originality, geographic location, harvest time, preparation procedures, and storage. The reliability and high quality of the final product can be guaranteed to some extent by adhering to standard manufacturing technique. The limits of harmful microorganisms and pesticides are determined, and heavy metal contamination is evaluated, during the product's safety testing phase. Biologic analysis, such as asthma and food allergy *in vitro* and *in vivo* models, may also be used to guarantee safety and efficacy before clinical application in humans. Product quality control for antiasthma herbal medicine intervention (ASHMI) and food allergy herbal formula-2 (FAHF-2)[1,9-11] has been successful thanks to this combination strategy.

Pelargonium Sidoides

Pelargonium Sidoides' Influence on Human Immunity

The Zulu and Basuto people of South Africa traditionally used African geranium (*Pelargonium sidoides*). It has been suggested that *pelargonium* can help reduce cold and bronchitis symptoms in adults[12-14]. A randomized controlled study published in 2007[15] verified the effects of *pelargonium* in relieving cold symptoms. More studies

are needed to evaluate its efficacy in avoiding Upper Respiratory Tract Infections (URTIs) and in treating influenza-like illness (ILI) across a variety of population subsets. The product has a high safety profile, with only mild allergic reactions and stomach distress reported by users (ZucolTM, Abkit, Inc., NY, USA).

The herbal treatment EPs®7630, also known as "Kaloba®" and derived from the plant *Pelargonium sidoides* DC (The standard abbreviation for botanist Augustin Pyramus de Candolle) (*Geraniaceae*), is useful for treating acute bronchitis[16]. (*Geraniaceae*) is one of the few current herbal treatments for respiratory infections that has some indication of efficacy. For almost a century, it has been a standard treatment for both diarrhea and tuberculosis in South Africa[16,17]. He was so confident in its efficacy that he began selling it for tuberculosis therapy in England in 1904, and the reports of tuberculosis (TB) patients' treated with this remedy[17,18] quickly spread throughout France and Switzerland. Stevens concealed the plant's true identity until the 1970s, when it was finally recognized. Since 1991[16,19], "Umckaloabo" has been sold throughout Europe to treat bronchitis.

Possible effects of *Pelargonium sidoides* can be explained by plausible processes. EPs® 7630, an extract from the root, exhibits low antibacterial activity[20] but increases macrophage activity[21,22] and decreases group A *streptococci* binding to human epithelial cells[23,24]. It is effective against many respiratory viruses[25,26] and inhibits viral infection of human broncho-epithelial cells by decreasing expression of cell membrane docking proteins and increasing expression of host defense proteins[27]. Antitussive effects have been observed in animal models using mice and guinea pigs[16,28].

Human Immunology Clinical Trials Involving Pelargonium Sidoides

Although the overall quality of the evidence was judged low[29], *Pelargonium sidoides* root extract may be beneficial at treating symptoms of acute bronchitis in both adults and children. All symptoms, cough, and sputum production improved, although results were mixed across three small randomized controlled trials of acute bronchitis in adults[29]. By day 5[30], there had been a significant difference in the bronchitis severity score (BSS)[30]. The liquid formulation had the potential to be more beneficial than the pills. Regardless of dosage form, *Pelargonium sidoides* reduced symptoms. Although liquid formulations of *Pelargonium sidoides* may be more effective, it is unclear if they are more widely available than the tablet form. Some doubt exists concerning the relative acceptability of tablet and liquid forms due to the lack of direct comparative data[16].

The UK's National Institute for Health and Care Excellence (NICE)[31] recommends *Pelargonium* as a "self-care treatment" for those who want to try it; it has "limited evidence of some benefit for the relief of cough symptoms". a high-quality independent clinical trial[16] of *Pelargonium sidoides* root extract is warranted.

Otamaxivir® drops with its content (20 mg) of African geranium (*Pelargonium sidoides*), exhibits immunomodulatory, antiviral, antibacterial, and anti-inflammatory effects, while vitamin C (18 mg) contributes to immune defense by supporting various cellular functions of both the natural and acquired immune system. For adults and adolescents aged 11 and above, the suggested dosage is 30 drops (3 × 1.5 ml) three times a day. For children aged 4-10 years, 30 drops (2 × 1.5 ml) twice a day[32].

Echinacea Purpurea

Echinacea purpurea products prevent or treat URTI in adults[13,32]. Taking *E. purpurea* as a preventative measure has been shown[13,33] to reduce the risk of catching a cold by 58% and shorten its duration by 1.4 days (both statistically significant). In 2006, the *echinacea*'s effectiveness in treating URTIs was reviewed[34]. Additional thorough trials are indicated to be needed, even if *echinacea* was reported[33] that to be more effective than placebo as a therapy for URTIs. *Echinacea* may help prevent pediatric colds when taken during cold and flu season, according to a large randomized controlled trial[35]; however, *echinacea* does not appear to diminish the length or intensity of symptoms when used to treat colds in children[13,36].

Direct antiviral activity[37] has been observed *in vitro* against the influenza virus and the induction of pro-inflammatory cytokines by *echinacea*. The therapeutic significance of this finding in the prevention or treatment of influenza-like illness (ILI) requires further investigation. The quality of *echinacea* supplements sold in the US varies widely. The *Echinacea Madaus* (Madaus GmbH, Köln, Germany) utilized in the majority of the successful experiments is made from the *E. purpurea* species' aerial parts.

Otamaximun capsules with their content of *Echinacea purpurea* extract (150 mg), alleviate symptoms associated with the common cold and

influenza infections, support the immune system, and enhance overall resistance. Beta-glucan (100 mg), derived from yeast, acts as an immune system activator by stimulating white blood cells, which are responsible for the initial defense of the immune system. Zinc (5 mg) plays a role in the normal development and function of natural immune cells, while vitamin C (60 mg) supports immunity and exhibits antioxidant effects. It is recommended to take it twice a day with meals[38].

European Black Elderberry (Sambucus Nigra)

The common cold and upper respiratory infection (URI) are commonly treated with *Sambucus Nigra* (European black elderberry) juice, also known as the extract Sambucol® (PharmaCare US, San Diego, CA). Elderberry has been shown[13,39] to bind to the influenza H1N1 virus *in vitro,* preventing infection. Black elderberry extract (1-4 teaspoons daily for 3-5 days for adults) has been shown[40-42] to reduce the severity and duration of flu symptoms, as well as increase immunity to the virus. However, before elderberry is routinely recommended for preventing or treating ILI[43], more research is needed to confirm these effects in more diverse North American populations (including children). There is no evidence that elderberry extracts can be used to treat or prevent URTI. Although allergic responses have been reported[13], elderberry is typically well tolerated.

Otaimuzinc pastille, with its content of Elderberry extract, helps to alleviate symptoms of flu and the common cold while supporting the immune system. Zinc plays a role in the normal development and function of natural immune cells, while vitamin C supports immunity and provides antioxidant effects. Otaimuzinc, in the form of lozenges, is easy to use and can be carried with you at any time. It is flavored with natural flower honey for a delightful taste. The recommended dosage is 4 pastilles per day for individuals aged 11 and above[44].

Rhizome of Ginger

Ginger (*Zingiber officinale*) is a perennial plant that can get as tall as four feet in ideal conditions[45,46]. Its summer flowers are a yellowish green and its thin, glossy, brilliant green leaves are rarely seen. The rhizome is the edible and therapeutic portion of the plant. Common terminology for identifying commercial ginger varietals includes their place of origin. This herb is native to the tropical regions of Southeast Asia, India, Africa, and the West Indies, but it can be grown anywhere with adequate soil and sunlight[45].

Ginger has been used as a medicine for quite some time. It is one of the most well-known Chinese and Japanese medical herbs, and it is typically used for headaches, nausea, and stomach disorders, as well as colds[47]. "Spicy" and "hot," ginger is said to "warm the body and treat cold extremities, improve weak and tardy pulses, address pale complexions, and strengthen the body after blood loss[48]".

Both fresh ginger and dry powdered ginger are utilized in Indian food and Ayurvedic medicine[49]. Ginger's virya, or potency, according to Ayurvedic practitioners, is "hot." Ginger is believed to balance the doshas (the three organizing principles providing homeostasis in Ayurvedic medicine), alleviate the symptoms of colds and other viral infections, improve digestion, stimulate appetite, and reduce arthritis. To combat malaria and yellow fever, ginger has been utilized in Nigeria and other African nations. Treatment of urinary tract infections[50] has included its use in the West Indies.

Although the exact method by which ginger exerts its antiemetic effects remains uncertain, some[51-53] have hypothesized that it may have an effect on the digestive system. Several components of ginger inhibit serotonin type 3 receptors, suggesting a central nervous system involvement; however, this has not been convincingly demonstrated. *In vitro* studies[54,55] have shown that ginger has anti-inflammatory properties, possibly by blocking the cyclooxygenase and lipoxygenase pathways in the metabolism of arachidonic acid.

Although ginger's active ingredients are not yet fully understood, gingerols and shogaols have been isolated from studies[56] using lipophilic rhizome extracts. The vast majority of studies[52,57,58] have found that ginger improves GI motility. Platelet aggregation *in vitro* was dose-dependently reduced by aqueous extracts of the fresh rhizome[54]. Platelet prostaglandin endoperoxides and thromboxane B2 production were both considerably suppressed by the extract. However, after two weeks of daily ingestion, neither 15 g of raw ginger rhizome nor 40 g of cooked rhizome reduced platelet cyclooxygenase activity[59] in 18 healthy volunteers. Eight healthy volunteers were given a single 2-g dose of the dried rhizome, and the results[60] showed no clinically significant differences in bleeding time, platelet count, or platelet functionality compared to placebo.

It was not until a 1982 investigation by Mowrey and Clayson[61] that ginger was subjected to a clinical trial in the West. In a study[45] including 36 male and female college students who reported a high vulnerability to motion sickness, the effects of 940 milligrams of powdered ginger rhizome were compared to those of 100 milligrams of dimenhydrinate or placebo. When given 20-25 minutes before testing in a motorized spinning chair, ginger was more effective than dimenhydrinate and placebo for preventing motion sickness.

To avoid nausea and vomiting, ingesting 500-1,000 milligrams of powdered dry rhizome an hour before exposure has been found to be effective[62-64]. This is similar to 2-4 grams of fresh or candied rhizome, or roughly 1 inch of the material. The administration of 500-1,000 milligrams (mg) of powdered rhizome daily has been studied[55] for the treatment of arthritic conditions like rheumatoid and osteoarthritis.

In humans, ginger has never been linked to any negative reactions. For seven days at 2.5 g/kg/day, there were no negative effects in animal tests evaluating acute toxicity, while doses of 3-3.5 g/kg/day killed 10-30% of the animals[55]. Single 2-gram dosages of dried ginger rhizome did not have a clinically significant effect on platelet aggregation in healthy subjects[45,60].

Vitamins and Minerals to Boost the Immune System

Beta Glucan

Glucans belong to a class of biologically active natural compounds and development interest as a result of their potential uses as immunostimulant[65].

β-1,3-Glucans (henceforth referred to as glucan) are naturally occurring compounds that have been shown[66] to have profound effects on human health. They are examples of pathogen-associated molecular patterns (PAMPs; for a review, see Zipfel and Robatzek[66]), which are highly conserved structures shared by many different types of pathogens. In the 1940s, Shear et al[67] described a polysaccharide compound derived from the seaweed *Serratia marcescens*, which triggered tumor necrosis; this discovery marked the beginning of the use of polysaccharides as immunomodulators. Rathgeb and Sylvén[68] made the first attempt to determine the structure of this so-called Shear's polysaccharide. They concluded that the polysaccharide was made up of glucose residues based on methylation analyses and periodate oxidation. Polysaccharides obtained from more benign species like yeasts, mushrooms, or even bananas[69] have been the focus of immunomodulatory research because bacterial extracts and separated products can be harmful. In the course of immune system development, multicellular creatures picked up the ability to identify certain molecules as foreign, prompting a variety of defensive responses. Thus, from invertebrates to humans, every species encodes the ability to identify glucans[65,70,71].

Bohn and BeMiller[72] published a review of the literature on the subject of structure-functional activity relationships in respect to the biological activities of β-(1,3)-glucans. They emphasized the significance of the β-(1,3)-glucan backbone, but they also pointed out many glaring discrepancies in the published data on the impact of molecular weight, water solubility, the degree of 6-*O*-substitution by glucopyranosyl units, global chain conformation, and intermolecular associations on antitumor activity and the mechanisms involved by these glucans. However, there was no definitive determination. Writers interested in learning more about this topic might check out Novak and Vetvicka[73].

Studies[74-76] confirmed that glucan strongly stimulates the immune systems of many different animals and humans alike (including worms, bees, shrimp, fish, chicken, rats, rabbits, guinea pigs, sheep, goat, pigs, cows, primates, and more). As a result of this research, we know that glucans are one of the rare immunostimulants that are functional across the whole evolutionary tree. Glucan has been shown to aid in the defense of plants in a number of experiments[65,77,78].

The macrophage is the most important biological target of glucans because of its ability to stimulate cellular immunity. In the initial wave of research, glucan's role in providing immunity from infection was identified. Protective benefits of glucan treatment against Leishmania major, *C. albicans, T. gondii, S. suis, P. berghei, S. aureus, E. coli, M. corti, T. cruzi, E. vermiformis, B. anthracis,* and *B. pseudomallei*[65,79-91].

Vitamin C (Vitamin 6)

Ascorbic acid (vitamin C) is the most commonly thought nutrient to prevent respiratory viral infections. Prophylactic vitamin C supplementation (200 mg or more daily) does not reduce the incidence of URTI in most adults. However, according to studies[13], taking vitamin C supple-

ments has been associated to a 50% reduction in the chance of acquiring a cold in a subgroup study of 642 very healthy persons participating in highly physically strenuous activities (marathon runners, skiers, and soldiers on subarctic exercises). Vitamin C has also been found to reduce the duration of cold symptoms by 8 percentage points in adults and 14 percentage points in children.

Deficits in vitamin C has been shown[92-94] to reduce the effectiveness of the immunological response to influenza virus infections in male mice. Vitamin C has moderate *in vitro* antiviral action against influenza virus. Supplemental vitamin C may help to prevent or treat seasonal or atypical influenza, although there are no clinical studies to back this claim[13].

Vitamin C can cause diarrhea and stomach pain if taken in amounts higher than 3 to 6 grams per day, but otherwise has a tolerability profile not dissimilar from that of placebo. In children and healthy adults subjected to physical stress, vitamin C appears to be most effective as a preventative agent to shorten the duration of URTI symptoms. There is not enough evidence to advocate its usage for prevention or treatment of ILI[13], and it does not seem to be helpful once symptoms have begun.

Zinc

Zinc, an essential mineral, is crucial for proper immune system function. Many enzymes rely on zinc for their structure, and it also acts as an intracellular signal between immune cells[13,95]. Zinc regulates the functioning of nearly every type of immune cell, and a lack of it can impair both humoral and cell-mediated immunity, leaving the body more vulnerable to infection.

Pneumonia is more common in people with low zinc levels, and it tends to be more severe. Zinc supplementation has been proven[96,97] to reduce the prevalence of pneumonia in children in underdeveloped countries. Zinc supplementation reduced the occurrence of acute lower respiratory tract infections in children by about 15%, according to a meta-analysis of studies[98]. More research in healthier populations is needed to determine if zinc supplements are useful in preventing or treating influenza-like diseases.

Zinc supplementation (15 mg daily for 7 months) was not related with a reduction in the prevalence of upper respiratory illnesses[99] in a 2009 research of healthy Air Force cadets. Children who took a zinc gluconate glycine lozenge (Cold-EEZE®), according to open-label research[99], experienced a 25% reduction in the duration of cold symptoms. Positive effects of zinc supplementation were found[100-102] in those people who started taking it soon after their symptoms started and who utilized products without citric or tartaric acid. Zinc may not be any more effective than a placebo in treating the common cold, according to a meta-analysis[103] published between 1996 and 2006. In a more recent randomized controlled trial[103], zinc supplementation significantly reduced symptom severity but not duration in Turkish children who began supplementation soon after cold symptoms arose. A second recent study used zinc lozenges (13.3 mg of zinc acetate every 2 to 3 hours while awake) or a placebo in a randomized controlled experiment including adults. Both the severity and duration of symptoms decreased in the zinc group, and no serious side effects were reported[13,104,105].

Lozenges made from zinc gluconate and glycine are generally well tolerated and safe[103]; however, there are side effects like a metallic taste, nausea, and stomach distress in some users. Lozenges pose a choking hazard and should not be given to children under the age of three. Zinc-containing nasal swabs and sprays have been linked[106] to anosmia (loss of sense of smell) and should be avoided pending the results of more research.

Zinc lozenges and nasal swabs are not the same as homeopathic zinc medicines, which are extremely diluted solutions that are normally very safe[13].

Although zinc supplementation does not appear to lessen the risk for upper respiratory infections in healthy, well-nourished populations, it nevertheless seems sensible to avoid zinc deficiency. Lozenges have shown inconsistent results in lowering the length and severity of already-present URTIs. Zinc nasal gels and swabs may be safe to use, however lozenges may not be. While homeopathic zinc remedies are risk-free to use, there is no evidence from clinical trials showing that they are effective in preventing or treating URTI or ILI[13].

We advise against taking zinc due to its dubious advantages and recognized bad effects, especially irreversible anosmia when delivered intranasally, even if zinc formulations may reduce the severity and duration of cold symptoms. There is some evidence from systematic reviews[107-109] that zinc intake is correlated with a shorter duration and milder intensity of cold symptoms. Higher

zinc levels (more than 75 mg daily) were found to shorten the duration of cold symptoms compared to lower doses (less than 25 mg daily) in a systematic review[108]. Zinc was found to shorten the time adults experienced symptoms (mean difference -1.65 days, 95% CI -2.5 to -0.8) in a meta-analysis[109]; however, there was substantial heterogeneity between trials. Negative side effects, such as nausea and a metallic taste in the mouth, were common in the zinc group across all studies[109].

The FDA issued a public health statement[110] warning against the use of Zicam and other zinc-containing intranasal medications due to repeated complaints of irreversible loss of smell. In addition to oral zinc supplements, intranasal zinc gluconate is also available as a homeopathic remedy for the treatment and prevention of the common cold. Hyposmia and anosmia have also been linked[111] to this formulation. Syrups and lozenges containing zinc sulfate have been demonstrated[112] to be more well-tolerated than some tablet forms.

Conclusions

Herbal remedies are undoubtedly valuable in boosting impaired immune function, particularly where damage has occurred due to malnutrition, chronic disease or previous infections. At present, however, an invincible immune[113,114] system remains firmly in the realm of fantasy. Herbal therapies like Otamaxivir® drops[32], Otamaximun capsule[38], Otaimuzinc pastille (Otacı, Kurtsan Ilaçları, Istanbul, Turkey)[44], which include these compounds, can be used to support standard medical care for patients with cough.

Conflict of Interest

Author Ayda Senol works in Otacı, Kurtsan Ilaçları, Istanbul, Turkey. The other authors declare that they do not have any conflict of interest with this paper.

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