SIMPLIX Ingredient Research Summary

There is substantial evidence indicating that diet and nutrition play significant roles in modulating the risk factors associated with cold and flu infections. In recent years, there has been a growing focus on the impact of micronutrients in the field of respiratory health, particularly concerning cold and flu viruses. To explore this, we conducted a comprehensive review of existing literature up until 2022, aiming to elucidate the effects of micronutrients, minerals, and vitamins on the course of cold and flu infections. Our review encompassed studies primarily focused on evaluating dietary supplements. Various natural compounds and micronutrients have shown potential in bolstering immunity and combating cold and flu infections at different stages, from initial exposure to the development of symptoms. Healthcare providers should be well-versed in this research and incorporate these findings into their counseling sessions with patients. Furthermore, there is a need for further meticulously designed investigations to provide precise guidelines for clinical practice in the prevention and management of cold and flu infections.

Ingredient	Data for Ingredient	Reference
Vitamin B12	This study investigated the relationship between serum levels of zinc, 25(OH)D, and vitamin B12 in 293 COVID-19 patients at the time of admission and their clinical outcomes. The research, conducted in a hospital in Iran, revealed that patients who died had lower levels of these micronutrients	https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.27277
	In B-12-deficient mice, the study examined immunological factors such as serum C3, IgM, IgG, IgE levels, and splenocyte expression of certain markers. B-12 deficiency led to decreased C3, IgM, and IgG, while IgE levels were significantly higher. Administration of CH3-B-12 showed a tendency to reverse these effects. B-12 deficiency also caused a shift in T cells from T helper type 1 to T helper type 2, contributing to elevated IgE production and altered CD4+CD8–/CD4–CD8+ ratio. This study suggests that B-12 plays a vital role in maintaining immune function in mice.	https://econtent.hogrefe.com/doi/abs/10.1024/0300-9831.71.1.60
	Patients with B12 deficiency showed decreased lymphocytes, CD8+ cells, and altered CD4/CD8 ratio, along with suppressed NK cell activity. Methyl-B12 treatment increased lymphocyte counts and CD8+ cells, improved CD4/CD8 ratio, and enhanced NK cell activity. The study suggests that vitamin B12 plays a crucial role in cellular immunity, particularly in relation to CD8+ cells and NK cell system	https://pubmed.ncbi.nlm.nih.gov/10209501/
	SARS-CoV-2, the virus behind COVID-19, belongs to the Coronaviridae family with a positive-sense single-stranded RNA genome. The genome encodes the nsp12 protein, housing RNA-dependent-RNA polymerase (RdRP) activity for viral replication. Methylcobalamin (vitamin B12) was found to bind to the nsp12 active site, potentially inhibiting RdRP activity by preventing RNA and nucleotide association. Computational studies suggest methylcobalamin could effectively inhibit nsp12.	https://pubmed.ncbi.nlm.nih.gov/32812340/

	In a study focusing on older COVID-19 patients, a combination of vitamin D, magnesium, and vitamin B12 (DMB) was investigated. After administering DMB to eligible patients, it was observed that fewer treated patients needed oxygen therapy during hospitalization compared to the control group (17.6% vs. 61.5%).	https://pubmed.ncbi.nlm.nih.gov/33039952/
Vitamin C	In a 5-year randomized controlled trial conducted in a Japanese village with participants diagnosed with atrophic gastritis, daily vitamin C supplementation of 500 mg significantly reduced the frequency of common colds compared to a low-dose group (50 mg)	https://www.nature.com/articles/1602261
	In a study involving 168 volunteers, those who received a vitamin C supplement (two tablets daily) over a 60-day period between November and February experienced significantly fewer common colds, fewer days challenged by viral infections, and a shorter duration of severe symptoms compared to the placebo group. The active-treatment group had 37 colds compared to 50 in the placebo group, with a significantly shorter duration of	https://link.springer.com/article/10.1007/BF02850271
	The study investigated the effects of daily oral administration of vitamin C (500 mg) alone or in combination with vitamin E (200 mg) on various immune functions in healthy elderly individuals. The research aimed to address immunosenescence, the age-related	https://www.sciencedirect.com/science/article/pii/S0531556520304666?casa_token=2aOm4ARfjJ0AAAAA:uORya_rZUsU6JiMHS
	The study examined the effects of vitamin C (1g) and vitamin E (200mg) daily supplementation on immune functions in aged women, including those with major depression disorders (MDD) and coronary heart disease (CHD). The 16-week supplementation significantly increased lymphoproliferative capacity and phagocytic	https://cdnsciencepub.com/doi/abs/10.1139/y98-038
	In this study, fucoidan, a polysaccharide derived from brown seaweed, was investigated for its immunomodulatory effects on dendritic cells (DCs), essential antigen-presenting cells. Fucoidan treatment enhanced DC viability, interleukin-12, and tumor necrosis factor-α production, and increased the expression of key immune molecules such as major histocompatibility complex class I, class II, CD54, and CD86. These findings indicate that fucoidan has immunostimulatory and maturing effects on DCs.	https://www.sciencedirect.com/science/article/pii/S0165247807002830?casa_token=ilg7PESKYxsAAAAA:UWIr7Tqbsfn7_1lEiUeMSIOMYeEyEu9cg3l0E-O-igz9k_q98yPCwVpKHRZjIyLoQQyIpSSaeQ

Seaweed	The study investigated the anti-influenza A virus (IAV) activities of fucoidan KW derived from brown algae Kjellmaniella crassifolia. KW effectively blocked IAV infection in vitro with low toxicity, displaying a broad spectrum of anti-IAV activity and low tendency for viral resistance induction. KW inactivated virus particles, inhibited viral neuraminidase (NA) activity, and interfered with multiple cellular pathways involved in IAV infection, including EGFR, PKCα, NF-κB, and Akt. Intranasal administration of KW improved survival and reduced viral titers in IAV-infected mice, suggesting its potential as a novel nasal drop or spray for influenza prevention and treatment.	https://www.nature.com/articles/srep40760
	Two low molecular weight fucoidan fractions from Laminaria japonica (LMW fucoidans) were studied for their antiviral properties in vitro and in vivo. In vitro, they demonstrated significant antiviral activity against various viruses in middle and high doses. In vivo, LMW fucoidans prolonged the survival time of virus-infected mice and improved lung conditions. Both LMW fucoidans enhanced immune responses, including thymus and spleen indices, phagocytosis, and humoral immunity, indicating their antiviral effects by enhancing immune functions.	https://link.springer.com/article/10.1007/s11802-018-3794-1
	Fucoidan enhances the probiotic effects of LAB (lactic acid bacteria) on immune functions. In vitro experiments using Peyer's patch cells and spleen cells demonstrated that fucoidan increased interferon (IFN)-γ production. In an in vivo study, oral administration of both fucoidan and LAB improved Th1/Th2 immunobalance in mice. These findings suggest that fucoidan can enhance the beneficial effects of LAB on immune functions.	https://www.spandidos-publications.com/ijmm/29/3/447
	The results showed that fish fed the diet with 0.4% fucoidan enhanced the growth, immune response, blood characteristics, and oxidative stress resistance.	https://link.springer.com/article/10.1007/s10695-018-0575-0

	The study investigated the efficacy and safety of iota-carrageenan (IC) nasal spray in preventing SARS-CoV-2 infection in advanced in vitro models of the human respiratory epithelium. The research confirmed that IC effectively protects reconstituted nasal epithelium from viral infection and replication of a patient-derived SARS-CoV-2 strain.	https://www.sciencedirect.com/science/article/pii/S2405580821002818
	Iota-carragenan is a polymer derived from red seaweed. In a study involving 153 children with acute symptoms of common cold, a nasal spray containing iota-carrageenan was compared to a placebo spray. The study found no significant difference in total symptom scores between the two groups from days 2 to 7. However, the iota-carrageenan group showed benefits in reduced time to clearance of the disease (7.6 vs 9.4 days), decreased viral load, and lower incidence of secondary infections with	https://link.springer.com/article/10.1186/1472-6882-12-147
	The combination of the anti-influenza drug Zanamivir with the antiviral polymer carrageenan has shown synergistic effects against various influenza A virus strains in vitro. In animal studies with lethal influenza viruses, the combined treatment significantly increased survival rates compared to individual treatments or a placebo, even when administered up to 72 hours post-infection.	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0128794
	This study investigated the relationship between serum levels of zinc, 25(OH)D, and vitamin B12 in 293 COVID-19 patients at the time of admission and their clinical outcomes. The research, conducted in a hospital in Iran, revealed that patients who died had lower levels of these micronutrients	https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.27277
	Zinc administered within 24 hours of the onset of common cold symptoms reduces the duration of symptoms, but caution is needed due to data heterogeneity. Zinc lozenges at a dose of ≥75 mg/day significantly reduce cold duration	https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001364.pub4/abstract

Zinc	A systematic review and meta-analysis of 17 randomized controlled trials involving 2121 participants evaluated the efficacy and safety of orally administered zinc for the treatment of the common cold. The analysis revealed that zinc supplementation reduced the duration of cold symptoms by an average of 1.65 days compared to placebo, although there was high heterogeneity in the results.	https://www.cmaj.ca/content/184/10/E551.short
	A randomized double-blind placebo-controlled trial involving 200 school-aged children in a low socioeconomic area of Iran found that zinc supplementation (10 mg elemental) significantly reduced the frequency of common cold episodes during the cold season. The zinc-supplemented group had 1.37 episodes per child compared to 3.15 episodes per child in the	file:///C:/Users/Pranav/Downloads/92320090406.pdf
	The study aimed to assess the effectiveness of prophylactic zinc sulfate administration in reducing the occurrence, duration, and severity of common cold symptoms in children. Two hundred healthy children were randomly assigned to receive either oral zinc sulfate or a placebo for seven months. The zinc group experienced fewer colds, with a mean of 1.2 compared to	https://onlinelibrary.wiley.com/doi/abs/10.1080/08035250600603024
	In a randomized, double-blind, placebo-controlled study, zinc gluconate lozenges significantly reduced the duration of common cold symptoms. Patients in the zinc group experienced a shorter time to complete resolution of symptoms (median 4.4 days vs. 7.6 days in the placebo group). The zinc group also had fewer days with symptoms such as cough, headache, hoarseness, nasal congestion, nasal drainage, and sore throat compared to the placebo group.	https://www.acpjournals.org/doi/abs/10.7326/0003-4819-125-2-199607150-00001
Lysine	Different groups of chicks were given varying amounts of Lysine and Methionine in their diet. The results showed that higher levels of these amino acids led to increased lymphocytes and decreased stress indicators in the blood. Additionally, there was a rise in antibody levels	https://d1wqtxts1xzle7.cloudfront.net/37979238/ABR-2012-3-7-3218-3224-libre.pdf?1435056553=&response-content-disposition=inline%3B+filename%3DEffect_of_Excess_Lysine_and_Methionine_o.pdf&Expires=1696198528&Signature=JO-cTGBq64c~DsKd3kZUTEzjffl9jO6ExXZ6Q-kHemO1Pz6G1e0Td46FfHQrAAvkiHajn7QC8SWZh63zMxxot76Xh48beAEavz18jul

	This review from 2022 discusses the relationship between the amino acid L-lysine and the control of viral infections, exploring its potential therapeutic properties. The research indicates that L-lysine can interfere with the formation of viral capsid proteins and DNA by competitively antagonizing the essential amino acid arginine, vital for some viruses. This interference may impact viral adhesion, fusion, and protein production, key factors in viral epidemiology and control.	https://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/bcp.15444
Shiitake Mushroom	In this study, 52 healthy individuals consumed either 5 or 10 grams of dried Lentinula edodes (shiitake) mushrooms daily for 4 weeks. The study aimed to assess the impact on immune function. Results showed that mushroom consumption led to increased proliferation and activation of immune cells (γδ-T and NK-T cells). These cells also exhibited improved effector function. Additionally, there was an increase in gut immunity (sIgA) and a reduction in inflammation (CRP levels). The cytokine secretion pattern also changed, indicating a less inflammatory	https://www.tandfonline.com/doi/abs/10.1080/07315724.2014.950391
	Mice pre-treated with lentinan (from shiitake) showed reduced parasitemia, increased survival, and boosted Th1 immune responses against malaria. Lentinan enhanced immune cell maturation, reduced regulatory T cells and IL-10 secretion, and prevented CD4+ T cell apoptosis.	https://www.sciencedirect.com/science/article/pii/S1567576909000253?casa_token=Y_0k5TwDTNAAAAA:aeA2CPXbgxmoUwsi93wTGdMoHSRgG3dzChZd
	The study analyzed extracts from Reishi, Shiitake, and Maitake mushrooms, focusing on β-glucan and α-glucan content. Three extracts were selected and combined into a formula. These extracts, especially in the combined formula, showed potent immuno-stimulatory effects in human macrophages. The formula demonstrated synergistic effects, particularly in cytokine expression, indicating a potential enhancement of immune response	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0224740&crsi=6624973112&cicada_org_src=healthwebmagazine.com&cicada_org_mdm=direct#sec011
	This review conducted in 2023 highlights the research and therapeutic potential of Shiitake. Shiitake contains essential minerals, vitamins, polysaccharides, antioxidants, and sterols, offering various health benefits such as antimicrobial, antiviral, anticancer, anti-obesity, antidiabetic, antioxidant, hepatoprotective, and immunomodulatory effects	https://www.sciencedirect.com/science/article/pii/S0924224423000821?casa_token=jdySdieO5acAAAAA:JjOwyBoYJAFeG_moK7SpPn_LYmh7SjfnHV9QsjKMvfVCq-sSLVf5qrBA7nX9kqBD7IgMKM5BZQ

	The study investigated the immunopotentiating effects of lentinan, a purified (1→3)-β-D-glucan extracted from the mushroom Lentinus edodes. In oral administration to mice, lentinan demonstrated increasing levels of lymphocytokines like IFN-γ, TNF-α, IL-2, and IL-1α. Lentinan activated immune cells in tissue cultures, particularly T-helper cells, making the host more resistant to cancer and infections.	https://www.dl.begellhouse.com/journals/708ae68d64b17c52,40f85691198060b9,18a80e4444b3833e.html
Andrographis	In a randomized double-blind study in Chile, 158 adult patients were divided into two groups, one receiving Andrographis paniculata SHA-10 extract and the other a placebo for 5 days. Patients evaluated symptoms such as headache, tiredness, earache, sleeplessness, sore throat, nasal secretion, phlegm, frequency, and intensity of cough. Results showed that by day 2, the Andrographis group experienced significant reductions in tiredness, sleeplessness, sore throat, and nasal secretion compared	https://www.sciencedirect.com/science/article/abs/pii/S0944711399800129
	In a randomized placebo-controlled double-blind study conducted during the winter season in a rural school, the preventive effect of Kan Jang tablets, made from Andrographis paniculata dried extract, against common colds was investigated. Students were divided into two groups, with one group receiving Kan Jang tablets and the other receiving a placebo. After three months, the Kan Jang group showed a significant decrease in the incidence of colds compared to the placebo group. The rate of cold	https://www.sciencedirect.com/science/article/abs/pii/S0944711397800517
	In a randomized, double-blind, placebo-controlled study, the efficacy of KalmCold™, an extract of Andrographis paniculata, was evaluated in patients with uncomplicated upper respiratory tract infection (URTI). Patients were assessed using a Visual Analogue Scale to score symptoms including cough, expectoration, nasal discharge, headache, fever, sore throat, earache, malaise/fatigue, and sleep disturbance. The study involved 223 patients who received either KalmCold™ (200 mg/day) or	https://www.sciencedirect.com/science/article/pii/S0944711309003201?casa_token=tIAKE-Ayyc0AAAAA:AmLh5adXG7gOKS_6XI4a_4Sm2qzxq5_ed5dOhC9WjyABynMBf53BrlPnWz4ei6YaTN7IMleWqQ
	The study aimed to evaluate the effectiveness of Andrographis paniculata in treating uncomplicated upper respiratory tract infections. A systematic review and meta-analysis of randomized controlled trials were conducted. The analysis included 433 patients from three trials. Andrographis paniculata in combination with Acanthopanax senticosus was found to be more effective than placebo, with a significant reduction in symptom severity scores	https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2710.2003.00534.x

Glycyrrhiza	A 26-year-old woman with acute sinusitis was treated using Glycyrrhiza glabra (licorice) tincture. She received 12 to 15 drops of a 2,000-mg tincture of licorice twice a day, resulting in significant improvements. Her symptoms, including facial pressure, soreness, headache, fever, and congestion, resolved within 3 days of treatment. This suggests that licorice may be an effective natural remedy for acute sinusitis.	https://www.sciencedirect.com/science/article/pii/S1556370717300913?casa_token=WX196oDnznYAAAAA:K7W38ex2FfiMNKfsns0IHZvVEspCClpdzYfsrw70Kcw1Q7BQJJwLN4HATQtwH7q8mOXoWxuyvg
	In a study with 57 European patients with chronic hepatitis C, glycyrrhizin therapy was administered intravenously thrice weekly for 4 weeks. Serum ALT decreased by 15% within 2 days and continued to decrease, reaching a mean of 26% by the end of treatment, higher than the placebo group's 6% decrease.	https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1440-1746.1999.02008.x
	The review highlights the potential of Glycyrrhiza glabra L. (Licorice) in managing respiratory infections due to its immune-modulating, anti-inflammatory, and antiviral properties.	https://www.ingentaconnect.com/content/ben/mrmc/2022/00000022/00000011/art00004
	This pilot study investigates the immune-activating properties of three herbs, Echinacea purpurea, Astragalus membranaceus, and Glycyrrhiza glabra, in human subjects when ingested orally. The study, conducted over 7 days, measured the activation of immune cells using flow cytometry, focusing on the CD69 marker. The results indicate that these herbal tinctures stimulate immune cells, particularly CD4 and CD8 T cells.	https://onlinelibrary.wiley.com/doi/abs/10.1002/ptr.1938?casa_token=zEF3z23pP8IAAAAA:U7TJkGltmV-cxo73EnvRAX5XShHPOwafUDFqsXCUwvaYQQ81OG_8ov7R96fwEo-NJMhjU9h0ojTdNIs

	The study aimed to assess the immune and antioxidant effects of Glycyrrhiza glabra polysaccharides (GGP) in rats fed a high-fat diet. The experiment involved four groups of mice, showing a significant reduction in serum antioxidant enzyme activities in the high-fat group. Treatment with GGP significantly enhanced both immune	https://www.sciencedirect.com/science/article/pii/S0141813009000695?casa_token=ye1qD0LYq7AAAAAA:UVvdm2RPEtP8F4a-TfKXcsfeC47GOcADn4GFzlq
	In this study, the effectiveness of phytochemicals found in Yashtimadhu (Glycyrrhiza), an Indian Ayurvedic herb, against key proteins of the SARS-CoV-2 virus was explored using molecular docking. The study focused on the Main Protease (Mpro), Spike (S) protein, and RNA-dependent	https://europepmc.org/article/ppr/ppr158774
Melissa officinalis	This review highlights all the research until 2023 that has indicated lemon balm's effectiveness against viruses like SARS-CoV-2, HSV, and HIV by inhibiting viral binding and replication processes.	https://journals.sagepub.com/doi/full/10.1177/11786388221146683
	In a study on rainbow trout, dietary supplementation with lemon balm extract (Melissa officinalis) at various doses improved growth parameters such as final weight, weight gain, and specific growth rate. The extract also enhanced immune responses, including increased white blood cell count and improved antioxidant enzyme activities like SOD and GPx. Lemon balm extract positively influenced digestive enzymes and reduced oxidative stress, indicating its potential as a growth-promoting and immunostimulatory supplement	https://link.springer.com/article/10.1007/s10695-019-00737-z
	The study analyzed the immune response in mice using an extract from Melissa officinalis. The extract was tested at different dilutions and administered orally and subcutaneously. The immunostimulating activity of the extract was compared with levamisole, a known immune system influencer. The results demonstrated the positive effect of Melissa officinalis leaf extracts on both humoral and cellular immune responses in mice.	https://europepmc.org/article/med/15080594