Supplemental File S1 – Scoping reviews

Scope of the market to identify ingredients

The overall goal for this project is to "get ahead of the game" by identifying products and ingredients that are coming into the market and/or forecasted to contribute to increased sales in the immune health dietary supplement market. As such, the authors performed a scoping of the market to identify dietary supplement products and ingredients marketed for immune function in otherwise healthy adults.

The team compiled an internal database of the following ingredients listed in various sources:

- Vitamins, minerals, and botanicals with "immune" claims (Dietary Supplement Label Database (DSLD) Advanced Search – yielded 1742 products with such claims and 79 ingredients that were reported in 20 + products identified consisting of vitamins, minerals and botanicals)
- Top 20 ingredients ranked by immunity sales (Nutrition Business Journal 2020 Immune System Report – communications with journal staff)
- "Immune boosting" ingredients and dietary supplements that appeared in greater than 10% of webpage advertisements based on Google analytics during the 1st and 2nd wave of COVID (BMJ Report, doi:10.1136/bmjopen-2020-040989)
- Popular dietary supplements based on Google search trends related to immunity during the COVID March 2020 outbreak (Hamulka et al. Report, doi.org/10.3390/nu13010054)

Ingredients identified from these sources were first sorted with NBJ-identified ingredients based on (1) the market analysis projections and (2) ingredients listed in and overlapping the multiple sources, as identified above thereafter. Ingredients not mentioned in multiple sources but were identified as listed in more than 100 DSLD products were also considered. This strategy yielded 27 unique dietary supplement ingredients considered to be frequently contained in dietary supplement products with claims related to immune function. **(Table S1)**

Scope of the literature to understand what exists

The authors performed a scoping review to learn what exists in terms of systematic reviews/meta-analysis on the identified ingredients with claims for immune support. What are the types of populations studied, the aims of the research conducted and related outcomes reported?

This exercise was to obtain a general sense of what research exists in terms of these select ingredients related to "immune." Findings helped to inform discussions with the Steering Committee as they relate to the ingredients, aims, and the selection of important outcomes for evaluating the evidence base.

PubMed was searched in July 2021 using MeSH mapping/all fields strategy for each ingredient coupled with "immun*." 548 citations were screened in Covidence at the abstract level based on a broad PICOS (population, ingredient, comparator, outcome, study design as described in **Table S2** below). Studies were excluded for the following reasons. These exclusionary criteria were only for the purpose of scoping the literature and do not dictate eligibility for the subsequent systematic review. For example, while we excluded pregnant and children for the purposes of scoping the literature, we may not do so for the systematic review.

- Did not include adult populations (18+)
- Included pregnant women in relation to their offspring
- Did not mention the dietary supplement ingredient or "immun*" in the abstract
- Focused on levels of vitamins and minerals in the body with no supplementation
- Not a systematic review or meta-analysis

Studies that passed the eligibility criteria were tagged according to the population, aim, and ingredient(s) reported. 159 citations moved to the data extraction phase accordingly. Studies published before 2015 were not included for the full extraction; as such, a total of 106 studies were reviewed. **(Figure S1)** Findings from this scoping were presented to the Steering Committee during a kick-off meeting. **(Tables S3-4)**

Table S1. Dietary supplement ingredients considered frequently contained in dietary supplement products with claims related to immune function

Ingredient	NBJ Market Analysis	DSLD Search for Immune Claims	Google Analytics - Immune Boosting	Google Trends-Immunity during COVID	Available as single ingredient product[1]
Echinacea	x	x		x	x
Elderberry	x	x	x	x	x
Garlic	x	x	x	x	x
Goji juice	x				x
Goldenseal	x	x			x
Mangosteen juice	x				x
Melatonin	x				
Mushrooms	x				x
Noni	x	x			x
Probiotics/Prebiotics	x		x	x	x
Slippery elm	x	x			x
Vitamin A	x	x	x		
Vitamin B	x	x			x
Vitamin C	x	x	x	x	x
Vitamin D	x	x	x	x	x

Zinc	x	x	x	x	x
Ginger		x	x	x	x
Turmeric/curcuma		x	x	x	x
Licorice		x		x	x
Selenium		x		x	x
Vitamin K		x		x	
Astragalus		x			x
Calcium		x			
Holy basil		x			x
Magnesium		x			
Rose hip		x			x
Vitamin E		x			x

[1]Available as single ingredient products on market for immune health (searched DSLD and Amazon)

Table S2. PICOS Eligibility Criteria for *broad* strategy to identify what already exists from systematic reviews

Eligibility Criteria	Broad Eligibility Used to Examine "What Exists"	Search Strategy
Population	Any adults (18+ years old), healthy or unhealthy	No initial restrictions to learn "what exists" on adult populations
Intervention	Any dietary supplement/ingredient defined as any product that met the following criteria: (a) any product (other than tobacco) intended to supplement the diet that contains one or more of the following ingredients: a vitamin, mineral, herb or other botanical, an amino acid, a concentrate, metabolite, constituent, extract or combination of any of these ingredients; (b) administered in any form (e.g., tablet, capsule, soft gel, gel cap, liquid, powder, gel, chews, skin patches/lotions/applications); (c) not represented as conventional food or as a sole item of a meal or of the diet (e.g., sport drinks, shakes, bars); (d) included a "Supplement Facts" rather than "Nutrition Facts" panel	27 select ingredients identified from DSLD, NBJ, Google trends and analytics search strategies chosen Specific ingredient names coupled with their scientific names and common names used to create search string or using MESH and all fields if such mapping exists. *Combination products included at this time. No restriction to "dietary supplements" in search strategy at this point*

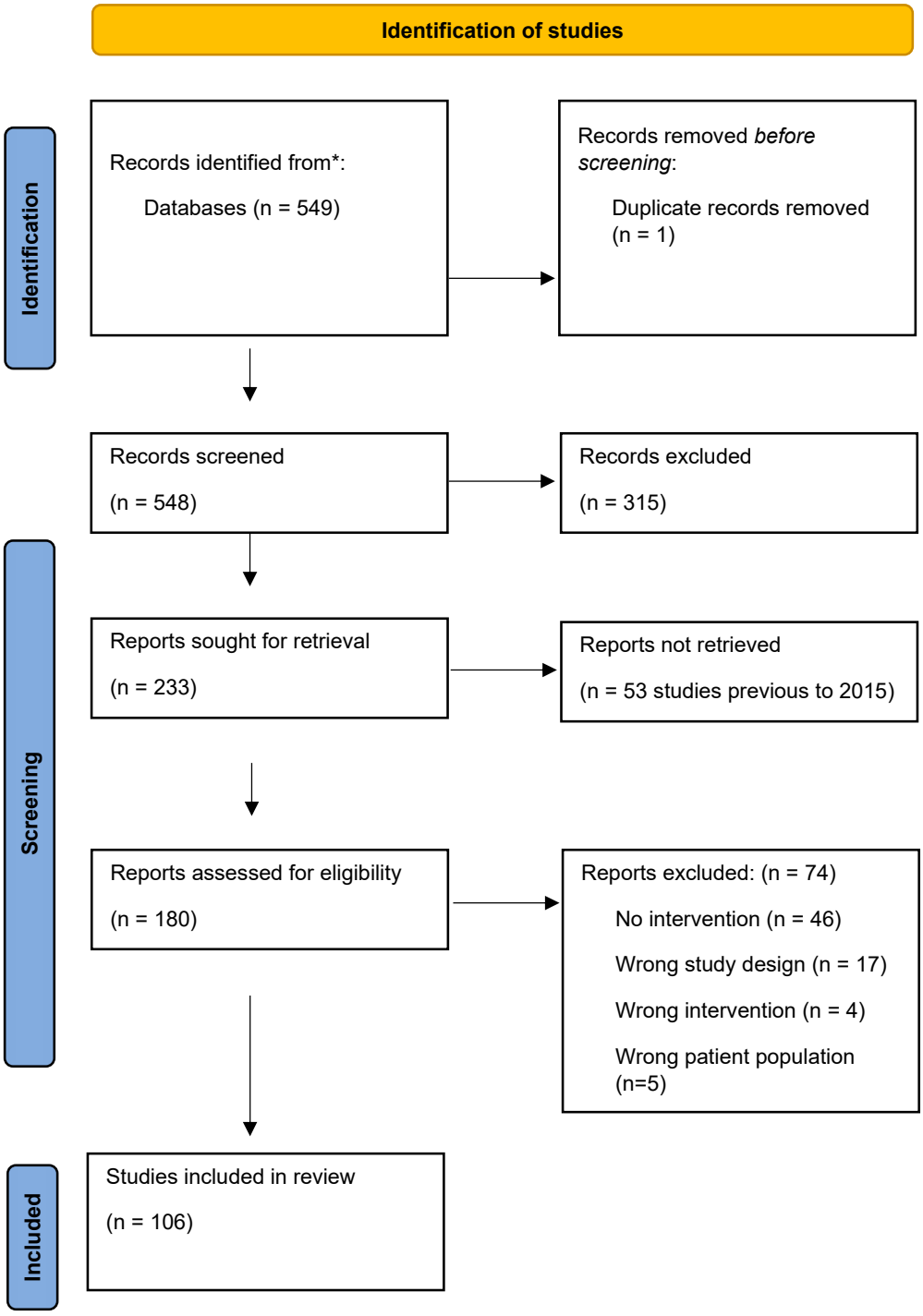
Control/ Comparator(s)	Sham (placebo), no treatment and/or active comparators	No restrictions for scoping
Outcome(s)	Immune function related outcomes	Any review that mentions immune in relation to the ingredient provided in the abstract considered to understand what exists. Search strategy included “immun*” in title/abstract
Study Design(s)	We will look for evidence first through quality Systematic Review and Meta-analyses for scoping the literature. Later, a full systematic review will be conducted to include other study designs	Search filters used to target systematic reviews/meta-analyses before moving into other study designs
Timing	We are interested in any timing	No restrictions for scoping

Search Strategy Executed in PubMed

(Echinacea or elderberry or garlic or goji berry or "goji juice" or goldenseal or hydrastis or mangosteen or garcinia mangostana or melatonin or mushroom or agaricales or noni or morinda or probiotic or prebiotic or slippery elm or ulmus or vitamin a or vitamin b or vitamin c or vitamin d or zinc or ginger or turmeric or curcuma or licorice or glycyrrhiza or selenium or vitamin k or astragalus or astragalus plant or calcium or holy basil or ocimum sanctum or magnesium or "rose hip" or rosehip or "Rosa"[Mesh] or vitamin e) AND (immun[Title/Abstract])*

Filters: Meta-Analysis, Systematic Review

Figure S1. PRISMA Flowchart



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table S3. Findings from Scoping Review of the Literature

This table displays the types of populations (i.e., healthy, those with respiratory condition, inflammatory condition, or another disease) reported among review articles for each select ingredient as well as the study's aim (i.e., prevention, treatment, performance/resilience).

Across all ingredients, 17% studies looked at otherwise healthy adults, including those under a stressor, vaccination, athletes, physically active individuals, and elderly; 24% studies looked at the prevention or treatment of respiratory conditions such as the common cold, viral and respiratory infections, influenza, coronavirus, allergic rhinitis, pneumonia, and tuberculosis; 25% studies looked at patients with inflammatory conditions such as atopic dermatitis, periodontal diseases, irritable bowel disease, ulcerative colitis, rheumatoid arthritis, and HIV; 30% unhealthy - other diseased including conditions such as cancer, liver disease, MS, cystic fibrosis and heart disease; and 4% of studies included data on safety and harms, with populations otherwise not specified. *Note that this scoping review only captured studies that included "immun*" in the titles/abstracts and is not representative of all studies for any condition.*

Ingredient	Healthy	Respiratory condition	Inflammatory condition	Unhealthy - other diseased
Astragalus			Treatment	
Calcium			Prevention; Treatment	
Combination formulations		Prevention; Treatment		
Echinacea				
Elderberry		Prevention; Treatment		
Garlic		Prevention; Treatment		Treatment
Ginger				
Goji				
Goldenseal				
Holy basil	Prevention			Treatment

Licorice				Treatment
Mangosteen				
Magnesium				Treatment
Melatonin		Prevention; Treatment	Prevention; Treatment	Prevention
Mushrooms				Treatment
Noni				
Prebiotics	Performance; Prevention	Prevention	Treatment	
Probiotics	Performance; Prevention	Prevention; Treatment	Prevention; Treatment	Prevention; Treatment
Rose hip				
Selenium		Prevention; Treatment	Treatment	Treatment
Slippery elm				
Turmeric			Treatment	Treatment
Vitamin A	Prevention	Prevention; Treatment	Treatment	Treatment
Vitamin B	Prevention	Prevention; Treatment	Treatment	Treatment
Vitamin C	Prevention	Prevention; Treatment		Treatment
Vitamin D	Prevention	Prevention; Treatment	Treatment	Prevention; Treatment
Vitamin E	Prevention	Prevention; Treatment	Treatment	
Vitamin K				
Zinc	Prevention	Prevention; Treatment	Treatment	Treatment

Table S4a. Outcomes Reported in Performance Studies

Across studies and represented in **Tables 4a-c**, biomarkers accounted for approximately half of outcomes reported on in the systematic reviews, with others related more toward clinical-type outcomes. Some of the most common biomarkers were c-reactive protein (CRP), interleukins (ILs), interferons (IFN), tumor necrosis factor (TNF), immunoglobulins (Ig), and cytokines across the different types of studies. Some of the most common other types of outcomes were related to symptom onset, symptom duration, severity, mortality and adverse events/safety. Most commonly reported are in bold throughout the tables below.

Population	Biomarkers	Other
Healthy	cellular innate immune activity **C-reactive protein (CRP)** **cytokines** detection of probiotics in stool immune markers immunoglobulins: SIgA inflammatory markers **interferons (IFNs)** **interleukins (IL)** metabolic markers NK cell tumoricidal activity prostaglandins **TNF/TNF-a** **white blood cells: monocytes, phagocytes,** **lymphocytes, macrophages**	cognition frailty gastrointestinal symptoms immune system modulation/performance mood **performance (time to exhaustion)** physical strength receipt of care

Table S4b. Outcomes Reported in Prevention Studies

Population	Biomarkers	Other
Healthy	blood glucose blood lipids: CD3, CD4 **C-reactive protein (CRP)** creatine kinase (CK) levels **cytokines** detection of probiotics in stool **immunoglobulins: IgA, IgE, IgG, IgM** inflammatory markers **interferons (IFNs): IFN-g** **interleukins (IL): IL-4, IL-10** lipid profile metabolic markers NK cell tumoricidal activity **nutritional status markers** prostaglandins **TNF, TNF-a** vaccines responses **white blood cells: monocytes, lymphocytes,** **phagocyte, macrophages**	adverse events blood pressure **cognitive function** digestive health **disease symptoms** frailty gastrointestinal symptoms general well-being **infections** insulin sensitivity/resistance microbiota composition mood mortality neurocognitive changes **nutrient dietary intake** **receipt of care** **vaccine performance**
Respiratory condition	**allergy markers** biochemical markers **cellular changes** **c-reactive protein (CRP)** **cytokines** endothelial function hemagglutination inhibition (HI) antibody titers **interleukins: IL6** immune cell phenotype **immunoglobulins: IgE** **immunological outcomes** **immunological response to vaccination** **inflammatory serum markers** interferons (IFNs) lymphocyte serological response **TNF** viral load	absences due to disease **adverse events** clinical manifestations compliance **disease duration** **disease episodes** **disease severity** **disease symptoms** **disease/infection occurrence** **hospitalizations - incidence/duration** ICU - admission **incidence of viral RTIs** **infection - incidence/risk** **medication usage** mortality number of sick days quality of life risk of complications side effects time to improvement ventilation/intubation - incidence/duration
Unhealthy	cholesterol - HDL, LDL, total triglycerides (TG)	**disease onset** **disease progression**

	immunoglobulins: IgE	ICU - duration incidence of delirium pulmonary function risk of symptoms symptom management symptom severity
Inflammatory	antioxidant status blood glucose carbohydrate metabolism cell proliferation composition of the intestinal microbiota **c-reactive protein (CRP)** **cytokines** immune responses insulin sensitivity **interleukins** metabolic activity of the intestinal microbiota metabolic stress oxidative stress **TNF**	adverse events BMI **clinical symptoms** fat mass inflammation intestinal barrier function production of compounds with anti-carcinogenic activity remission/relapse symptom management tumor growth

Table S4c. Outcomes Reported in Treatment Studies

Population	Biomarkers	Other
Respiratory condition	**allergy markers** **cellular changes** **c-reactive protein (CRP), hs-CRP** **cytokines** erythrocyte sedimentation rate (ESR) hemoglobin **immunoglobulins: IgA, IgE** **inflammatory markers** **interferons (IFNs): IFN-g** **interleukins: IL-6, IL-10** plasma levels serum levels **TNF** **white blood cells: monocytes, lymphocytes, neutrophil**	**adverse events** **BMI** **body measurements** chest imaging clinical deterioration cognitive function **condition-specific symptoms** **cure** **disease duration** **disease incidence** **disease severity** dyspnea fatigue **hospitalization - duration/incidence** **ICU admission - duration/incidence** infection/illness insomnia medication use **mortality** pain physical function **quality of life** radiological examinations risk of complications sick days TB score time to improvement time to recovery vaccine response ventilation/intubation - frequency/incidence
Unhealthy	adiponectin anti-tumor immune response blood lipid profile (cholesterol: HDL, LDL, total) **c-reactive protein (CRP), hs-CRP** creatine kinase (CK) levels **cytokines** endotoxin **Glucose measures** glutathione peroxidase (GSH-PX) glycemic measures **immune function parameters** **immunoglobulins: IgA, IgE, IgG, IgM**	adverse events balance blood pressure body weight bone disease-related outcomes CHD mortality clinical status disease activity disease complication **disease duration** **disease incidence** **disease onset** **disease progression**

	inflammatory parameters insulin sensitivity measures **interferons (IFNs)** **interleukins: IL-6, IL-10** leptin lipid profile NK-cell activity nutritional status markers serum levels **TNF** triglycerides (TG) **white blood cells: T-lymphocytes**	**disease severity** **disease-related symptoms** disorder status fatigue **health-related quality of life** hepatic fibrosis hepatic function hospitaliation - duration ICU - duration immune depression immune function/response immunological status-related outcomes infections liver function long-term survival malignant transformation **mortality** need for additional therapy neurocognitive changes performance status/score pulmonary exacerbations pulmonary function quality of life relapse rates respiratory status-related outcomes risk of illness tumour response ventilation - duration wound healing
Inflammatory	antioxidant status blood glucose carbohydrate metabolism **CD4 + cells** C-reactive protein (CRP) **cytokines** erythrocyte sedimentation rate immunomodulatory effects insulin sensitivity **interleukins: IL2, IL-6, IL-10, IL-12** metabolic stress oxidative stress indices: antioxidant capacity, malondialdehyde serum levels serum thyroid peroxidase (TPOAb) Th17Treg cells thyroglobulin (TgAb) autoantibody levels **TNF**	body mass index diarrhea management **disease activity** **disease progression** **disease severity** fat mass hypovitaminosis infection levels/risk **mortality** oral lesions pain severity remission/relapse rates safety swollen joint count symptom management tender joint count **nutrient dietary intake**

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