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Food Supplements in the Pediatric Population of Serbia: A Review of Commonly Used Products

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Abstract

Food supplements (FS) are products intended to provide additional nutrients to the normal diet. They contain concentrated amounts of nutritive and non-nutritive compounds with a nutritional or physiological effects and are available in various dosage forms for ingestion in small, defined quantities. In recent decades, FS have become increasingly popular among children. When developing pediatric products, both the nutritional needs and the safety aspects specific to this population group are considered. This report analyzes dietary supplements used by children in Serbia, focusing on dosage, safety and the existence of official guidelines. The analysis includes vitamins (D, K and B-complex), probiotics, omega-3 fatty acids, beta-glucans and various herbal products. Although these supplements are widely used in Serbia, there are official pediatric guidelines only for vitamin D, vitamin K, probiotics and omega-3 fatty acids. Herbal supplements are particularly problematic due to insufficient data on safety, interactions and possible side effects. Therefore, increased education of both parents and healthcare professionals is essential to ensure appropriate intake, maximize health benefits and support the proper and safe use of supplements in the pediatric population.

Key words: food supplements, pediatric population, guidelines, vitamins, herbal preparations

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Introduction

Food supplements (FS) are products intended to provide additional nutrients to the regular diet. They contain concentrated amounts of nutrients or other substances with nutritional or physiological effects and are available in various dosage forms, such as capsules, pastilles, tablets, oral powders, oral solutions, oral drops, or other similar forms of liquids or powders, for intake in small, defined quantities (1). FS may include a wide range of vitamins, minerals, amino acids, herbs, essential fatty acids, dietary fibre, probiotics and enzymes (2). The regulation of FS in Serbia is harmonized with that of the European Union (3), with the primary aim of protecting consumers from potential health risks and ensuring that information provided is accurate and not misleading.

In recent decades, demographic growth and ongoing industrial development have coincided with increased demand for dietary supplements. Modern life, often marked by irregular eating habits and increased stress, has created a need for practical sources of nutrients and bioactive compounds. Simultaneously, advances in food processing and formulation technologies have enabled the industrial-scale production of these supplements, contributing to their steady global increase in availability and use. The COVID-19 pandemic further intensified interest in dietary supplements as potential adjuvants in both the prevention and treatment of the disease (4).

The use of FS is rising, specifically within the pediatric population (5). Nutritional requirements, and thus the need for supplementation, vary with age and overall health status, with the first year of life characterized by higher demands than later childhood. In infancy, exclusive breastfeeding is considered optimal, while routine vitamin K is administered at birth. Children under three years of age are usually supplemented with vitamins D and K, omega-3 fatty acids, probiotics and prebiotics to support optimal growth and adequate immune system development. Vitamins, minerals, and other bioactive compounds (e.g., beta-glucan) are commonly used during specific periods of the year, for example, in winter (6). Furthermore, FS are also used as adjuncts in the management of various medical conditions, including hyperactive/attention deficit disorder (ADHD), common colds, asthma, infantile colic, cancer, and epilepsy (7).

This paper provides an overview of the most commonly used FS in the pediatric population in Serbia, highlighting both their potential benefits and adverse effects. In addition, the discussion addresses regulatory aspects and the current status of official recommendations. Ultimately, this review aims to contribute to a more rational and evidence-based use of food supplements in children.

Vitamin D

Vitamin D is a fat-soluble micronutrient essential for maintaining human health, occurring naturally in two primary forms: vitamin D_3 (cholecalciferol), which originates from animal sources, and vitamin D_2 (ergocalciferol), found in certain plants and fungi. In humans, vitamin D_3 can also be synthesized endogenously in the skin through the photochemical conversion of 7-dehydrocholesterol when exposed to ultraviolet B radiation

from sunlight. Despite this endogenous capacity, modern lifestyle factors such as limited outdoor activity, use of sunscreen, higher latitudes, and seasonal variations often restrict adequate cutaneous synthesis (8, 9). Without supplementation, many individuals do not meet recommended intake levels (9–11).

Traditionally recognised for its pivotal role in bone growth, mineralization, and remodeling, vitamin D is indispensable for maintaining calcium, phosphorus, and magnesium homeostasis. It enhances intestinal absorption of these minerals, supports normal bone turnover, and helps prevent skeletal disorders. Beyond these skeletal effects, accumulating evidence highlights its wide-ranging extra-skeletal benefits. Studies have demonstrated antimicrobial properties, adjustment of immune activity and a reduced risk of developing diabetes mellitus and autoimmune thyroiditis. Furthermore, vitamin D appears to improve cardiovascular health by supporting endothelial function and regulating blood pressure, inhibits abnormal proliferation of malignant cells, modulates hormone secretion, stimulates nitric oxide synthesis, protects neural tissue, and contributes to the reduction of migraine frequency (8, 12).

The most serious manifestation of vitamin D deficiency in children is rickets, a metabolic bone disease characterized by defective mineralization of the growth plate. While historically rare in developed countries, its incidence has been increasing in parts of Europe over the last decade, with prevalence estimates ranging from 4% to 7% among children aged 1–6 years (9, 10).

Although human milk is regarded as the optimal standard for infant nutrition, its vitamin D concentration is typically low (<50 IU/L) (9). Consequently, the European Academy of Paediatrics (EAP) and other relevant international health organizations recommend that all infants up to 12 months of age receive a daily oral supplementation of 400 IU of vitamin D, as a universally accepted measure to prevent rickets and ensure proper bone health. The same dose is recommended by the Serbian Association of Paediatricians, demonstrating consistency with European and international recommendations and emphasizing the importance of harmonized preventive practices in child health care. Regular testing for vitamin D deficiency in healthy children is generally not advised, except for those in high-risk groups, including individuals with darker skin pigmentation, chronic liver or kidney disease, limited sun exposure, or conditions associated with malabsorption. After the age of one, vitamin D may be recommended for children in these high-risk populations (13).

The National Institute for Health and Care Excellence (NICE) specifically advises drops containing vitamin D for babies and toddlers (14). Current evidence suggests that supplementation beyond 400 IU per day in healthy infants does not confer additional health benefits (10).

For children over one year of age, supplementation strategies vary internationally. The EFSA recommends intake of 600 IU per day for individuals aged 1–17 years (15). According to the European Academy of Paediatrics, the recommended dietary intake is suggested to be 400 to 600 IU per day for healthy children and adolescents, accounting factors such as seasonal variation in sunlight exposure, skin pigmentation, dietary intake, or specific

medical conditions. Fortified milk consumption between the age of 2 and 6 has been shown to be a safe and effective measure to prevent insufficiency during the winter months or in regions with reduced sunlight (10, 12).

The tolerable upper intake level (UL) for vitamin D varies by institution. The EFSA has established a UL of 1,000 IU per day for infants and 2,000 IU per day for children aged 1–10 years (15). Exceeding these limits, particularly through the uncontrolled use of over-the-counter supplements, can result in vitamin D toxicity, leading to hypercalcemia and hypercalciuria. Acute symptoms include abdominal pain, anorexia, fever, nausea, and diarrhea, whereas chronic excessive intake may cause soft tissue calcification, nephrocalcinosis, kidney stones, metabolic bone disorders, dehydration, weight loss, and neuropsychiatric disturbances such as confusion and psychosis (8, 12).

Vitamin K

Vitamin K is a fat-soluble micronutrient that occurs naturally in two principal forms. Vitamin K_1 (phylloquinone) is predominantly found in green leafy vegetables, whereas vitamin K_2 (menaquinones) is produced by certain gut-resident bacteria and is also present in fermented foods (16).

Vitamin K plays a central role in numerous physiological processes, most notably in blood coagulation and bone metabolism. Functioning as a cofactor for the enzyme γ-glutamyl carboxylase, it is necessary for activating several vitamin K-dependent proteins in the coagulation cascade, such as prothrombin and clotting factors VII, IX, and X. Beyond its hepatic functions, vitamin K is indispensable for the activation of osteocalcin, a protein essential for bone mineralization, and matrix Gla protein (MGP), a potent inhibitor of vascular calcification. Increasing evidence suggests that optimal vitamin K status may be associated with a reduced risk of osteoporosis, arterial stiffness, type 1 diabetes, and certain cardiovascular and pulmonary disorders (16, 17).

Recommended dietary intakes vary with age, sex, and physiological condition. The European Food Safety Authority (EFSA) has set adequate intake (AI) values at 10 µg per day for infants and 12 µg per day for young children (18). While overt deficiency is rare in healthy adults due to both dietary availability and endogenous synthesis by intestinal microbiota, certain populations remain at high risk, most notably newborns. Limited placental transfer, low hepatic stores at birth, and immature gut flora contribute to the susceptibility of infants to vitamin K deficiency bleeding (VKDB), which may manifest as bleeding from the umbilical stump, gastrointestinal tract, skin, or, in severe cases, intracranial hemorrhage. VKDB is classified according to onset: early ($\leq$ 24 h after birth), classic (within the first week), or late (up to 6 months of age) (19).

To prevent VKDB, major health authorities recommend universal prophylactic vitamin K_1 administration shortly after birth, typically a single 1 mg intramuscular dose within the first 6 hours of life, or an oral regimen over the first weeks. In particular, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends a single intramuscular (IM) dose of 1 mg administered at birth, or oral alternatives consisting of three doses of 2 mg given at birth, 4–6 days, and 4–6 weeks, or a

weekly 1 mg oral dose for 3 months following an initial 2 mg dose at birth. Classic VKDB is more common in breastfed infants as a result of the limited vitamin K content in human milk (~ 2.5 µg/L) compared with formula (24–175 µg/L). Without prophylaxis, VKDB occurs in approximately 0.6% of newborns, most often within days of delivery; timely administration is highly effective in preventing both early- and late-onset forms (20, 21). In Serbia, the Republic Expert Commission on Maternal and Child Health in 2014 recommended that prophylaxis of hemorrhagic disease of the newborn should begin with intramuscular administration of vitamin K1 immediately after birth (1 mg in term infants, 0.5 mg in preterm infants). Due to the documented risk of late hemorrhagic disease, the Commission also recommended extended oral prophylaxis with 25 µg vitamin K1 daily from the second to the twelfth week of life in exclusively breastfed infants and in specific risk situations (prolonged jaundice, antibiotic exposure, maternal use of antiepileptics or antibiotics) (22). In older children, deficiency is uncommon but can arise in conditions involving fat malabsorption (e.g. cystic fibrosis, coeliac disease, chronic pancreatitis), prolonged use of broad-spectrum antibiotics, or chronic liver disease. In such cases, targeted supplementation is warranted, with dosing adjusted to the underlying pathology and severity (17).

Toxicity from natural forms of vitamin K is exceptionally rare, and the EFSA has not established a tolerable upper intake level (UL) due to the absence of adverse effects in healthy individuals. However, the synthetic analogue vitamin K_3 (menadione) has been linked to oxidative stress and hemolytic anemia and is not recommended for human supplementation (16).

Vitamin B complex

Vitamin B complex (B1, B2, B3, B5, B6, B7, B9, B12) plays an important role in supporting metabolic processes essential for normal body function, including the metabolism of fats, carbohydrates, and proteins at various stages. Vitamin B1 (thiamine pyrophosphate, TPP), vitamin B2 (riboflavin, sodium riboflavin-5'-phosphate) and vitamin B3 (nicotinamide, nicotinic acid), contribute to normal energy metabolism. Vitamin B6 (pyridoxine hydrochloride, pyridoxine-5'-phosphate, pyridoxine dipalmitate) contributes to maintaining adequate immune system function, participating in all reactions of amino acid metabolism as well as in the synthesis of antibodies. Vitamin B5 (pantothenic acid) contributes to normal mental performance, while vitamin B7 (biotin) is involved in gluconeogenesis, the synthesis of fatty acids, the breakdown of amino acids. Vitamin B9 (folic acid; 5-methyltetrahydrofolate, 5-MTHF) is involved in the biosynthesis of purine and pyrimidine bases, which are essential for the formation of DNA and RNA molecules. Vitamin B12 (methylcobalamin and 5-deoxyadenosylcobalamin) plays a key role in the formation of red blood cells, DNA synthesis and maintaining a healthy nervous system (23). Thus, vitamin B12 deficiency is associated with impaired cognitive development, while megaloblastic anemia in a child can result from vitamin B12 or folic acid deficiency. Vitamin B6 deficiency is resolved by administering pyridoxine or pyridoxal-5'-phosphate. In infants and neonates with an inborn pyridoxine metabolic defect, seizures can be severe

and refractory, but typically respond to pyridoxine administration. Lack of vitamin B3 in children leads to memory lapses and skin irritation. Similar effects can result from deficiencies of vitamins B1 and B2. Lack of vitamin B2 can also cause angular cheilitis (23).

For infants and toddlers, minimum and maximum levels of vitamins in baby food are expressed per 100 kcal or 100 kJ (24), while nutritional reference values (NRVs) are prescribed for the vitamin content of food supplements (25).

Although B complex vitamins are necessary and their levels are reduced in certain health conditions (e.g. coeliac disease) (26), supplementation with these vitamins is underused. There are no data in the literature, or the available data are insufficient to conclude that vitamin B complex supplements improve health condition. As a result, official guidelines for the supplementation of B-group vitamins in the pediatric population have not yet been established. Although these vitamins are widely recognized as essential for normal growth and development, the absence of national guidance means their use is generally left to clinical judgement and individual healthcare practice.

Probiotics

According to the definitions provided by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO), probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host (27). Traditionally, the most commonly used probiotics are lactic acid bacteria (LAB), the best-known genus being *Lactobacillus* (in 2020, the genus *Lactobacillus* was revised and divided into 23 new genera) and *Bifidobacterium*. The yeast *Saccharomyces boulardii*, as well as certain species from the genera *Escherichia coli* and *Bacillus* are also used as probiotics, and among these, there are strains with well-studied effects. Although LAB, which have been used for thousands of years to preserve food by fermentation, may also have potential health-promoting effects, the term “probiotic” should be reserved exclusively for live microorganisms that have been shown to provide health benefits in controlled human studies, as required by the definition of probiotics (28). Probiotic strains exert health effects through one or more known mechanisms of action. They can influence the intestinal ecosystem by modulating the immune response of the mucosa, stimulating specific and non-specific immune responses, interacting with commensal or potentially pathogenic microorganisms, producing metabolites such as short-chain fatty acids, and through chemical signaling with host cells. Some mechanisms of action are common to several strains, but the therapeutic effects are always strain-specific. Through these mechanisms, probiotics can improve the intestinal environment, strengthen the intestinal barrier, exert antagonistic effects against potential pathogens, reduce the inflammatory response, and enhance the immune system’s response to antigenic challenges. These processes are thought to underlie most of the beneficial effects of probiotics, including the reduction of the frequency and severity of diarrhea from various causes, alleviating colic in infants, reducing symptoms associated with lactose maldigestion, and preventing allergies, among others (28).

Probiotics are increasingly administered in pediatric populations, although some uncertainty remains regarding their optimal and justified use. Therefore, the European

Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has published revised recommendations for the use of probiotics in the pediatric population for the prevention and treatment of selected gastrointestinal disorders (29). The recommendations are based on an updated review of randomized controlled trials and an evaluation of the quality of the evidence, with a clear statement of the indications for the use of probiotics in the pediatric population. The recommendations with moderate certainty of evidence are summarized in Table I. Indications such as acute gastroenteritis, prevention of necrotizing enterocolitis in preterm infants, and *Helicobacter pylori* infection were omitted from the table owing to the low or very low certainty of the available evidence. Other indications, including functional constipation, coeliac disease, small intestinal bacterial overgrowth, and inflammatory bowel disease, which have also been considered by the ESPGHAN, are likewise excluded, as no official recommendations have been issued to date.

Table I ESPGHAN recommendations for the use of probiotics in the pediatric population (2023)

Tabela I Preporuke ESPGHAN-a za upotrebu probiotika u pedijatrijskoj populaciji (2023)

Indication	Recommended strain / dose/ duration	Certainty of evidence/ grade of recommendation*
Prevention of Antibiotic-Associated Diarrhea	*S boulardii** or *L rhamnosus* GG started simultaneously with antibiotic treatment dose: ≥ $5x10^9$ CFU/day	moderate / strong
Prevention of Nosocomial Diarrhea	*L rhamnosus* GG for the duration of the hospital stay for the prevention of nosocomial diarrhea in children dose: ≥ $5x10^9$ CFU/day	moderate / weak
Management of infant colic in breastfed infants	*L. reuteri* DSM 17938 dose: ≥ 10^8 CFU/day duration: 21 day	moderate / weak
	B. lactis BB-12 dose ≥ 10^8 CFU/day duration: 21–28 days	moderate / weak
Functional abdominal pain disorders	*L. reuteri* DSM 17938 dose: 1-2x10^8 CFU/day for pain intensity reduction in children with functional abdominal pain disorders	moderate / weak
	L rhamnosus GG dose: 1-3x10^9 CFU twice daily for the reduction of pain frequency and intensity in children with irritable bowel syndrome	moderate / weak

*According to the GRADE system

Based on the ESPGHAN document, the Neonatology Section of the Serbian Paediatric Association has developed national recommendations for the use of

probiotics in the pediatric population, adapted to local conditions and available probiotic products (30).

Regarding the use of probiotics for the prevention of allergies in children, the European Academy of Allergy and Clinical Immunology (EAACI) states in its guidelines that it is neither in favor of nor against the use of probiotics for this purpose, as there is insufficient evidence (31). The American Academy of Pediatrics, the National Institute of Allergy and Infectious Diseases, and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition also do not advise using probiotics to prevent allergic diseases (32). However, in 2015, the World Allergy Organization (WAO) conditionally recommended their use in pregnant women, breastfeeding women and infants at high risk of allergy, although this was based on very weak evidence, particularly for the prevention of eczema (33).

A positive and expected outcome of the proposed recommendations can be achieved only by using products with a verified declared composition and quality. Therefore, in its revised 2023 guidelines, the World Gastroenterology Organisation (WGO) states that the labeling of probiotic products should include: the name of the genus, species and strain (according to current nomenclature), the number of viable microorganisms at the end of shelf life, the recommended dose based on proven effects, the recommended storage conditions, a precise description of the physiological effect (according to the legal framework), and contact information for post-marketing surveillance (28). The Serbian Association of Paediatricians particularly emphasizes the importance of applying GMP standards in the production of probiotics for children, especially for premature babies (30).

Probiotics used in food supplements are generally considered safe for the healthy pediatric population. However, their use is contraindicated in pediatric patients with severe immunodeficiency or critical illness due to the potential risk of fungemia or bacteremia.

Omega-3 fatty acids

Long-chain polyunsaturated fatty acids (LC-PUFAs) play a key role in maintaining cell membrane fluidity, structural organization, and optimal physiological function in the body (34). Linoleic acid (LA, 18:2n-6) and α-linolenic acid (ALA, 18:3n-3) are classified as essential LC-PUFAs, while their metabolic products include the LC-PUFA arachidonic acid (AA, 20:4n-6) and the LC-PUFAs eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) (34). Among LC-PUFAs, DHA is most abundant in the brain and plays a central role in membrane properties and signal transmission, particularly in the frontal lobe, which governs higher cognitive functions (35). The prenatal stage, especially the third trimester, is a critical period for n-3 LC-PUFAs in neurodevelopment. During the third trimester, fetal brain tissue, specifically the frontal cortex and hippocampus, undergoes a rapid increase in DHA, at an estimated rate of 70 mg per day, due to enhanced cellular synthesis (36). DHA supplementation during pregnancy has been associated with prolonged gestation,

higher birth weight, and improved neurodevelopmental outcomes. Concerns about mercury exposure from fish (the primary source of EPA and DHA) have led to the increased use of prenatal fish oil and n-3 supplements. Supplementation trials in infants have consistently shown positive associations between LC-PUFA intake and both cognitive and visual function, attributed to ongoing deposition in retinal tissue and the brain (36). Most studies have focused on DHA, often in combination with EPA and AA, due to their roles in neuronal membrane structure synapse maturation, and processing speed (37). Although the most rapid phase of n-3 accretion occurs in late gestation and the first 18 months of life, cognitive development continues throughout childhood and adolescence. During these later stages, LC-PUFAs remain important for brain maturation, synaptic plasticity, and functional connectivity. Research has increasingly examined their potential in mitigating neurodevelopmental disorders such as ADHD, phenylketonuria, and autism spectrum disorder (ASD) (36). The European Food Safety Authority (EFSA) recommends a daily intake of 250–500 mg of EPA and DHA for European adults to reduce the risk of cardiovascular disease (38). Infants and children up to 2 years of age should receive 100 mg of DHA daily, while those older than 2 years and adults are recommended 250 mg of combined DHA and EPA. Pregnant and lactating women are advised to supplement with an additional 100–200 mg of DHA per day on top of the standard adult dose (39).

Based on EFSA recommendations, the Serbian Association of Paediatricians updated its advice to ensure adequate DHA intake for breastfeeding mothers, suggesting a daily consumption of 200–400 mg of DHA (40). If the mother cannot achieve this intake, DHA supplementation should be given directly to the infant: exclusively breastfed infants are suggested to intake 100 mg DHA daily; infants breastfed and supplemented with formula (up to 250 mL/day) are recommended to receive 100 mg DHA every second day. For infants introducing non-milk foods after 4 months: exclusively or predominantly breastfed infants should receive 100 mg DHA daily, while infants mainly fed with formula should receive 100 mg DHA every second day (40). Evidence indicates that ensuring sufficient n-3 status during critical developmental periods, especially infancy and early childhood, may have long-term benefits for cognitive performance, cardiovascular health, and overall growth in children. Table II provides EFSA health claims and recommended daily intakes for DHA/EPA and essential fatty acids in the pediatric population.

Table II EFSA health claims with recommended daily intake for DHA/EPA and essential fatty acids

Tabela II EFSA zdravstvene izjave i preporučen dnevni unos za DHA/EPA i za esencijalne masne kiseline

	EFSA health claims	Recommended daily intake
Docosahexaenoic acid (DHA)	Intake of DHA during pregnancy and breastfeeding contributes to the normal development of the brain and eyes in fetuses and infants	200 mg of DHA per day, in addition to the recommended daily intake of omega-3 fatty acids for adults, e.g., 250 mg of DHA and EPA
Docosahexaenoic acid (DHA)	Intake of DHA contributes to the normal development of infants up to 12 months of age	100 mg of DHA per day
α-Linolenic acid (ALA) and linoleic acid (LA)	Essential fatty acids are necessary for the normal growth and development of children	2 g of ALA and 10 g of LA per day

β -Glucans

β-Glucans are heterogeneous, non-starchy polysaccharides, primarily water-soluble dietary fibers, composed of D-glucose monomers linked by β-1,3-1,4-glycosidic bonds or β-1,3-glycosidic bonds with various β-1-6 side-branches, which determine their different bioactivities. β-glucans are found in both non-cereal and cereal sources. Cereal β-glucans are characterized by a β-1,3-1,4 backbone without branching and can be divided into water-soluble and water-insoluble fractions (41). The structure of cereal β-glucans enables them to form gels and increase intestinal viscosity, which slows the digestion and absorption of nutrients, including glucose and cholesterol (42). This property led to the EFSA authorization of health claims for oat and barley β-glucans, confirming that their regular dietary use can help maintain normal cholesterol levels and control postprandial glucose levels. These health claims are also incorporated into national legislation in Serbia. Cereal β-glucans have prebiotic properties due to their fermentation by beneficial gut microbiota, resulting in positive changes in microbiome composition and the production of short-chain fatty acids (43).

However, β-glucans also exhibit anti-infective and immunomodulatory activity while demonstrating favorable safety profiles (44). Therefore, their use has been extended to pediatric populations, necessitating a comprehensive understanding of both their safety and efficacy profiles in children. Immunomodulatory activity is mainly associated with non-cereal fibers. Non-cereal β-glucans are commonly found in fungi, yeasts, bacteria, and algae and are characterized by 1-3 β-glycosidic linkages combined with β 1-6 side-branches (45). Polymers with medium and high molecular weight have greater immunomodulatory activity (46). The most studied and best described bioactive β-glucans are lentinan (from *Lentinus edodes),* ganoderan (from *Ganoderma lucidum*), scleroglucan (from *Sclerotium glucanicum*), pleuran (from *Pleurotus ostreatus*), and zymosan (from *Saccharomyces cerevisiae*) (47). Yeast and pleuran β-glucans are most

commonly used in dietary supplements for the pediatric population, in the form of a nasal spray or syrup (48).

The immunomodulatory properties of β-glucans arise from their ability to trigger both innate and adaptive immune responses through interactions with gut-associated lymphoid tissue and macrophage activation pathways. β-glucans preferentially bind to several pattern recognition receptors (PRRs), including Dectin-1, the CR3 receptor, Toll-like receptors (TLRs), scavenger receptors, and lactosylceramide (LacCer) (49). Binding to these receptors initiates intracellular signaling cascades, including the activation of nuclear factor kappa B (NF-κB) and the secretion of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1, IL-6, IL-8, IL-12), and other inflammatory mediators that enhance the immune response (44). Enhanced phagocytosis and antimicrobial defense with β-glucan supplementation are achieved by stimulating macrophages and neutrophils. Complement activation via CR3 stimulated NK cells. Recent evidence suggests that β-glucans induce epigenetic and metabolic reprogramming in monocytes and macrophages, a phenomenon known as trained immunity, leading to an enhanced and faster response to subsequent infections. By activating and maturing dendritic cells, β-glucans influence the adaptive immune system, promoting antigen presentation and stimulating B-cell and T-cell responses, thereby enhancing humoral and cellular immunity (49).

A review of pediatric studies using pleuran β-glucan formulations (10 mg/5 kg body weight/day) or yeast β-glucans (35–75 mg/day) found a significant reduction in the incidence or severity of respiratory tract infections (RTI), with excellent tolerability (49). Other studies reported increases in salivary immunoglobulins (IgA, IgM, IgG), lysozyme, and CRP following β-glucan supplementation compared to placebo (50). Extended clinical data supported improved mucosal defense, reduced inflammatory markers such as calprotectin, and general immune stimulation (51). A randomized, double-blind, placebo-controlled trial in asymptomatic children aged 3–5 years in Colombia, who received yoghurt enriched with β-glucan from *Ganoderma lucidum* for 12 weeks, reported significant increases in circulating lymphocyte populations: CD8+, CD4+, CD3+, and total lymphocytes (52).

EFSA is evaluating β-glucans for potential use as a novel food ingredient. The authority has outlined the use and recommended dosages of yeast beta-glucans for children, as detailed in the EFSA Journal (53). According to the EFSA, beta-glucans are considered safe at the proposed use levels for the general population when provided through food supplements (up to 375 mg/day) and foods specifically designed for nutritional needs (up to 600 mg/day). The main dosage recommendations from this document for children are:

- Infants (12 to 35 months): recommended intake ≤ 100 mg per day
- Older children (3 to 14 years) in food supplements: ≤ 750 mg per day
- Older children (3 to 14 years) in fortified foods: ≤ 500 mg per day

The EFSA also notes that yeast beta-glucans are not formulated for use in infant formula or follow-on formula. According to a separate authorization (54), the maximum amount of yeast beta-glucans permitted in food supplements for children under 12 years of age (excluding food supplements for infants and young children) is 0.675 g/day, and 1.275 g/day for children over 12 years of age and adults. Oat and barley β-glucans carry health claims for adults (cholesterol reduction), but not specifically for pediatric immune or general use; these are not EFSA-recommended doses for children.

Evidence indicates that β-glucans can reduce the severity and incidence of RTI, enhance mucosal immunity, and improve immune biomarkers in children, while demonstrating good safety profiles. However, further high-quality trials are needed to confirm efficacy and optimize dosing strategies in the pediatric population.

Herbal supplements

Food supplements containing herbal ingredients are mainly used in children to strengthen immunity and resistance during and after illness, during growth, and in cases of malnutrition, usually in combination with vitamins, minerals, oligosaccharides and other ingredients acting synergistically (55). Given that data on the consequences of using herbal ingredients are often lacking, and that various interactions with other foods and drugs may occur, as well as the potential for adverse reactions and certain quality control issues, the use of such products remains questionable in children of different ages and is generally not recommended in early childhood (infancy to 6 years of age) (56).

Some of the most common natural and herbal ingredients used in FS for the pediatric population for their immunomodulatory effects include Echinacea species (E. purpurea, E. angustifolia, E. pallida, Asteraceae), elderberry, pelargonium, acerola, royal jelly, and propolis.

Many products containing various types of *Echinacea* root extracts and/or *E. purpurea* herb juice are primarily intended for the supportive treatment of the common cold and various infections. Although clinical data supports the efficacy of these products and they appear to be safe and well tolerated, their use should be limited to the first signs of a cold and restricted to short periods (up to 10 days, several times a year), while long-term use should be discouraged. Additionally, due to insufficient data, they are not recommended for children under 12 years of age. Likewise, they are not recommended in cases of immune diseases (such as tuberculosis, collagenoses, multiple sclerosis, diseases of the white blood cell system, AIDS, HIV infections and others). Although adverse effects such as hypersensitivity reactions (rash, urticaria, itching, facial swelling, angioedema, Quincke edema, bronchospasm with airway obstruction, asthma and anaphylactic shock) are of unknown frequency, in sensitive individuals and atopic patients should consult a doctor before using *Echinacea* products due to the possible risk of allergic and anaphylactic reactions. Use is not recommended in individuals with hypersensitivity to the active ingredient(s) or to other members of the Asteraceae (Compositae) family (57).

Elderberry (*Sambucus nigra*, Adoxaceae) is rich in anthocyanins, flavonoids, organic acids, minerals, sugars and pectin. It also contains high levels of vitamins C, B and A (58). Elderberry has been shown to have antioxidant, antiviral, antibacterial, anti-inflammatory and immunomodulatory effects. In the past, juice and syrup made from fresh elderberry juice were used as purgatives and for treating colds and rheumatic complaints. Today, dry extracts and concentrated or lyophilized elderberry juice (standardized for anthocyanin or total polyphenol content) are mainly used in the form of syrups and oral solutions, intended to strengthen the body's resistance and immunity, and for sore throats, colds and flu (59). Dosage varies according to the type of preparation (Table III). It is used at the first signs of a cold and continued for several days.

Table III Some of the most commonly used herbal supplements in the pediatric population in Serbia

Tabela III Primeri najčešće korišćenih biljnih suplemenata u pedijatrijskoj populaciji u Srbiji

	Usage	**Preparation**	**Dosage/ Duration of use**	**Precautions**	**Contraindications**	**Adverse effects**
Elderberry (*Sambuci fructus*)	Strengthening the immunity and body resistance, in flu and common cold	Elderberry dry extract, standardized on 10% of polyphenols	Children 3-12 years: 100 mg 2x daily. Children over 12 years: 150 mg 2x daily. Several days.	Use in children under 3 years of age is not recommended. Caution is recommended with concomitant use of diuretics. Not recommended in compromised immune system conditions.	Hypersensitivity to the active substance(s).	Nausea, vomiting and diarrhea.
Pelargonium root (*Pelargonii radix*)	Common cold, upper respiratory tract infections.	Liquid extract (DER 1:8–10), extraction solvent ethanol 11% (w/w)	Children 3–6 years: 0.4 mL 3x daily Children 6–12 years: 0.9 mL 3x daily. Up to 7 days.	The oral use in children under 3 years of age is not recommended because of concerns requiring medical advice. In case signs of hepatotoxicity occur, the administration of the medicinal product should be stopped immediately, and a medical doctor should be consulted.	Hypersensitivity to the active substance(s).	Hypersensitivity, rash, pruritus, urticaria, angioedema, nasal bleeding, diarrhea, epigastric pain, nausea, vomiting, gingival bleeding, hepatotoxicity, hepatitis.
Acerola fruit	Source of vitamin C and carotenoids	Acerola fruit extract, standardized on 25% vitamin C	Children 3–12 years: 60 mg 2x daily. Children over 12 years: 90 mg 2x daily.	Maximum safe doses in young children, pregnant or nursing women, and people with severe liver or kidney		Diarrhea, cramping, dizziness or fainting, flushed appearance, frequent

Rosehip (*Rosae pseudofructus*)	Source of vitamin C and carotenoids	Rosehip extract, standardized on 45–70% of vitamin C	Children 3–12 years: 43 mg 2x daily. Children over 12 years: 64,5 mg 2x daily.	disease have not been established.		urination, headache, nausea, and vomiting. Prolongated use of high doses may raise concern in individuals with conditions that lead to iron accumulation in the body.
Propolis	Anti-inflammatory, immune-boosting activity.	Tincure 1:10	Five drops 2x daily (10 drops 1x daily) in water, juice, yogurt, milk.	Long term use is not recommended considering reports that propolis can alter estrogen levels and pose a risk for early puberty. Might slow blood clothing and increase bleeding time. Stop using 2 weeks before surgery. Might increase the risk of bruising or bleeding, due to interactions with anticoagulants and antiplatelet drugs.	Hypersensitivity to the active substance(s). Allergic predisposition, in particular an allergy to pollen.	Hypersensitivity reactions (itching, burning skin, urticaria, local rash, allergic cheilitis, gingivitis, contact dermatitis)
		Solution containing 20% propolis	Children 4–10 years: 10 drops daily. Children over 10 years: 20 drops daily.			
Royal jelly		Liophylized RJ	Children older than 3 years: 40–80 mg daily. Up to 2 months. For long term use medical doctor (pediatrician or immunologist) should be consulted	Hypersensitivity on bee products. Might increase the risk of bruising or bleeding and lowering blood pressure, due to interactions with warfarin and some antihypertensives.	Hypersensitivity to the active substance(s).	Hypersensitivity reactions (urticaria, eczema, rhinitis, bronchospasm and anaphylaxis; contact dermatitis)
Aniseed (*Anisi fructus*)	Cough in common cold and respiratory infections; Mild, spasmodic gastro-intestinal complaints including bloating and flatulence	Herbal tea	One to 3.5 g of the whole or (freshly) comminuted or crushed aniseed in 150 mL of boiling water as herbal infusion, 3x daily. Up to 2 weeks.	The use in children under 12 years of age is not recommended due to the lack of adequate data. Duration of use is limited for 2 weeks, because of the lack of available safety data on long-term use of aniseed preparations, and due to the presence of compounds such as *trans*-anethole and estragole.	Hypersensitivity to the active substance or to Apiaceae (Umbelliferae) (caraway, celery, coriander, dill and fennel) or to anethole.	Allergic reactions to aniseed affecting the skin or the respiratory system may occur.

Sweet Fennel (*Foeniculi dulcis fructus*) Fennel (*Foeniculi amari fructus*)	Cough in common cold and respiratory infections. Mild, spasmodic gastro-intestinal complaints including bloating and flatulence.	Herbal tea, dry extracts (0.1% of essential oil)	Children 4–12 years: 1.0 g of the herbal substance in 100 mL boiling water (steep for 15 minutes) as an herbal infusion, 3x daily. Up to 7 days. Children over 12 years: 1,5 g as an herbal infusion, 3x daily. Up to 2 weeks	Use in children under 4 years of age is not recommended due to a lack of data. The use in children between 4 and 12 years of age is not recommended if the daily intake of estragole exceeds the guidance value of 1.0 µg/kg bw, unless justified by a risk assessment based on adequate safety data. In children under 12 years of age, the daily intake of estragole has to be below 1.0 µg/kg bw.	Hypersensitivity to the active substance or to Apiaceae (Umbelliferae) family (aniseed, caraway, celery, coriander and dill) or to anethole. Hypersensitivity to mugwort pollen, due to cross-reactivity with fennel.	Allergic reactions to fennel, affecting the skin or the respiratory system may occur.

Various extracts of pelargonium root (*Pelargonium sidoides*, *P. reniforme*, Geraniaceae) are common ingredients in products used for colds and flu, sore throat, cough, and inflammation of the mucous membranes of the upper respiratory tract. The main active ingredients of the root and its extracts are tannins (gallic acid esters, oligomeric and polymeric proanthocyanidins) and oxidized coumarins. Clinical studies have confirmed the antibacterial, antiviral and immunomodulatory effects, as well as the safety of these products (60). They may be used in children over 3 years of age for up to 7 days from the first signs of a cold, while use in younger children is not recommended. Adverse reactions are rare (61).

Acerola fruit (*Malpigia* sp., Malpigiaceae) is very rich in macro- and micronutrients, vitamin C (1680 mg per 100 g of fresh fruit), as well as bioactive compounds (anthocyanins, flavonoids, phenolic acids, carotenoids, etc.). It has antioxidant and anti-inflammatory effects, and in supplements it acts as an antioxidant and stabilizer. Some evidence indicates better absorption and elimination of vitamin C from acerola fruit compared to the ascorbic acid alone (62). Rosehip (*Rosa* sp., Rosaceae) is also considered as an important natural source of antioxidants: vitamins C, E and carotenoids. It is usually used as an herbal tea (2–5 g of dry crushed rosehips in 150 mL of boiled water, 3–4 times daily) for the common cold, infections and inflammatory conditions, for making jellies, marmalade, nectars or wine (63). In supplements, acerola and rosehip preparations (juice, liquid extracts, powdered fruit pulp or acerola fruit extract, dry powdered rosehips or rosehips dry extracts) are usually standardized to vitamin C content. When using acerola and rosehips products, care should be taken regarding daily recommended intake (DRI) for vitamin C. Though water-soluble vitamin C has a low toxicity, long-term intake of doses above upper tolerable intake levels (ULs) (400–2000 mg, depending on age) can increase the risk of adverse effects (nausea, upset

stomach, constipation, and heartburn, and in some health conditions could exacerbate iron overload) (64).

Royal jelly (RJ) is used as food for the queen bee and is produced by worker honeybees (*Apis mellifera*, Apidae) as a milky secretion rich in carbohydrates, proteins, amino acids, fatty acids, vitamins, and minerals. In addition to these nutritionally important components, RJ also contains biologically active compounds such as 10-HDA (10-hydroxy-2-decenoic acid) (1–3%), peptides and proteins (royalactin, royalisin), and flavonoids. The composition of RJ varies depending on geographical origin, climate, bee species, plant species, season and collection method. To maintain its nutritive and biologically active components, RJ should be frozen immediately after collection. RJ is also used in lyophilided form, but differences between fresh RJ and lyophilized samples still need to be clarified (65). The efficacy of RJ has been shown in alleviating allergic symptoms and supporting various health aspects, including energy, immunity, cardiovascular function, and psychological well-being. Due to its high content of amino acids, gamma globulins, and other essential nutrients, it strengthens the immune system against viral infections and supports immune function during chemotherapy and radiotherapy (66). Due to its variable composition, the dosing of royal jelly depends on formulation, posology and intended use, as well as being influenced by individual factors (67). Some data suggest that RJ may increase the effects of warfarin and certain antihypertensives, potentially raising the risk of bruising or bleeding and lowering blood pressure. Royal jelly can cause hypersensitivity reactions, particularly in individuals sensitive to bee products, including urticaria, eczema, rhinitis, bronchospasm and anaphylaxis. Cases of contact dermatitis that worsened after oral or topical application of RJ have also been reported (68). The daily dose for adults depends on their condition, age and specific needs, and ranges from 3 to 10 g/day. Studies have shown that optimal effects may be achieved with a daily dose of 100 mg/kg. In children, RJ is used for malnutrition, loss of appetite, and to strengthen the immune and nervous systems. The dose is 0.5 g/day (children of 1–5 years of age) and 1 g/day (children of 5–12 years of age), either alone or in combination with other bee products. In cases of colds and acute infections, the daily doses are 2.5 g (children of 1–5 years of age) and 5 g (children of 5–12 years of age), for 1–3 days (67).

Propolis is brownish and sticky substance produced from resinous, gum-like and balsamic materials collected and transformed by bees. It is used to protect the hives from infestations with fungi, bacteria or other insects and to repair cracks in hives in order to maintain constant humidity and temperature (69). Main constituents are balsams and resins (50–55%), waxes (30–40%), pollen (5%), essential oils (5–10%) and other substances like phenolics (cinnamic aldehyde, flavonoids, coumarin, vanillin), sugars, vitamins and minerals (68). Although the composition of propolis varies greatly depending on botanical and geographical origin, it consistently exhibits well-known effects, including antioxidant, anti-inflammatory, antibacterial, antiviral, immunomodulatory, and anticancer properties. Artepillin C, pinocembrin, and caffeic acid phenethyl ester (CAPE) are recognized as the main active ingredients of propolis

from various sources. According to EU regulations, propolis may be used in food supplements only if it is extracted using approved solvents, without further refining or purification, so as to remain outside the scope of novel foods (70). General dosage recommendations for propolis supported by clinical trials are lacking. A daily dose of 70 mg or 1.4 mg/kg of propolis is considered safe for healthy individuals. However, practical dosing may be up to 400–1500 mg per day (71). Some animal studies showed that propolis may enhance fertility and promote growth in the ovaries and follicles of neonatal mice. There are also reports that propolis can reversely alter estrogen levels after prolongated use (2–3 months) (72). Propolis is a powerful sensitizer causing a well-recognized occupational allergic eczematous contact dermatitis in apiarists. According to some opinions, propolis is contraindicated in individuals with an allergic predisposition, especially in those allergic to pollen and other bee products (73).

Table III summarizes some of the most commonly used herbal supplements in the pediatric population in Serbia. Given the growing interest in safe and effective natural-origin products for children, more comprehensive and thorough investigations are necessary to identify the optimal application method with proven efficacy and reduced risks and side effects.

Conclusion

The use of food supplements in children in Serbia is becoming more common, but official pediatric guidelines are limited to certain bioactive substances such as vitamins D and K, probiotics and omega-3 fatty acids. Herbal supplements remain a particular challenge due to insufficient data on safety and potential adverse effects.

There is an increasing need for better education of both parents and healthcare professionals to ensure the appropriate use of food supplements and to achieve optimal health outcomes in children. Additionally, the development of national guidelines, further clinical research, and the implementation of policy measures would strengthen evidence-based practice and ensure consistent, safe supplementation across the pediatric population. Ultimately, promoting informed, evidence-based decisions regarding pediatric supplementation is essential for safeguarding child health and supporting optimal development.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

N.D., I.Đ.: Visualization, Formal analysis, Writing – original draft; J.K.M., O.D.P., T.I., M.D.: Methodology, Writing – original draft; NI – Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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Dodaci ishrani u pedijatrijskoj populaciji u Srbiji – pregled najčešće primenjivanih proizvoda

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Kratak sadržaj

Dijetetski suplementi (dodaci ishrani) su namirnice dizajnirane da dopune svakodnevnu ishranu. Oni sadrže koncentrovane izvore nutritivnih i nenutritivnih sastojaka sa hranljivim ili fiziološkim efektom i u prometu su u različitim farmaceutskim oblicima, namenjenim za konzumiranje u odmerenim pojedinačnim količinama. Poslednjih decenija, upotreba dijetetskih suplemenata je postala sve češća u pedijatrijskoj populaciji. Formulacije za decu su posebno dizajnirane kako bi se zadovoljile njihove nutritivne potrebe i specifični bezbednosni zahtevi. Ovaj pregledni rad sadrži analizu dijetetskih suplemenata koji su često u upotrebi kod dece u Srbiji, sa fokusom na doziranje, bezbednost i dostupnost zvaničnih smernica. Opisani su dijetetski suplementi koji sadrže vitamine (D, K i B kompleks), probiotike, omega-3 masne kiseline, beta-glukane i različite biljne preparate. Uprkos širokoj upotrebi u Srbiji, zvanične pedijatrijske smernice postoje samo za vitamin D, vitamin K, probiotike i omega-3 masne kiseline. Biljni suplementi i dalje predstavljaju poseban izazov zbog nedovoljno podataka o bezbednosti, interakcijama i potencijalnim neželjenim efektima. Uzimajući u obzir sve navedeno, neophodno je edukovati roditelje i zdravstvene radnike, kako bi se obezbedio adekvatan unos, osigurali optimalni zdravstveni efekti i omogućila bezbedna upotreba dijetetskih suplemenata u pedijatrijskoj populaciji.

Ključne reči: dodaci ishrani, pedijatrijska populacija, smernice, vitamini, biljni preparati