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Infant Nutrition: Breast milk substitutes and gut-brain axis improved by microalgae

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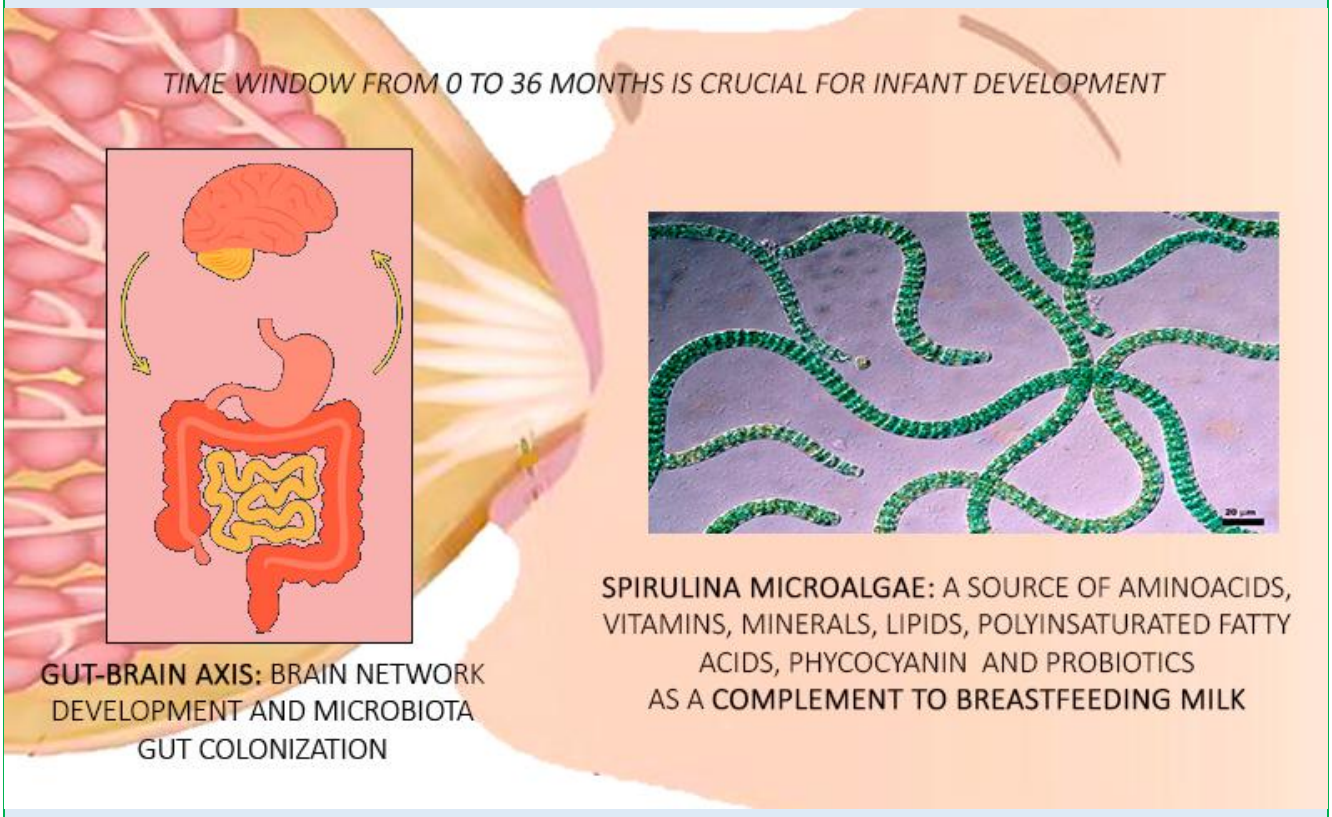
ABSTRACT

Nutrition during the early years of life is crucial for optimal development in babies, as this stage establishes important physiological processes such as growth, brain maturation, formation of the immune system, and the food absorption system. While breastfeeding is considered the ideal option, in some circumstances infant formulas are used as a supplement or substitute. In this context, the proposal to enrich these formulas with microalgae such as Spirulina and Schizochytrium emerges, which are rich in nutrients and beneficial bioactive compounds for health. Spirulina stands out as a concentrated source of proteins, vitamins, minerals, and other essential nutrients, while Schizochytrium sp. provides omega-3 fatty acids, especially docosahexaenoic acid (DHA), which is important for brain and visual development. Furthermore, the potential of microalgae and their beneficial properties are discussed, along with the reasons behind their underutilization in the past. Concerning natural and artificial breastfeeding, the importance of bacterial flora in nutrition and gut-brain health is examined. Balanced bacterial flora plays a crucial role in digestion, nutrient absorption, and maintaining overall health in both naturally-fed infants and those receiving infant formulas. In summary, the inclusion of microalgae in infant nutrition is presented as a promising strategy to improve the health and well-being of children in their early years. Fortifying infant formulas with microalgae can help meet the specific nutritional needs of infants, promote healthy growth, and prevent nutritional deficiencies, offering immunological, antioxidant, and neuroprotective benefits that support their optimal development.

Keywords: Breastfeeding, Infant nutrition, Schizochytrium sp, Spirulina, Microbiota.



INTRODUCTION.

Breastfeeding is the natural nourishment mechanism for newborns and infants that ensures the correct growth and development of the newborn. In addition to nutrients, breast milk contains bioactive compounds responsible for the maturation of the immune system, cognitive and locomotor development, and protection against infections. The World Health Organization (WHO) recommends exclusive breastfeeding for up to 6 months and, together with complementary feeding, for up to 2 years of age. However, when breastfeeding is not possible, artificial breastfeeding must be used. A high percentage of infants at 6 months (54.1%) and at one year of age (78.3%) are fed with infant formulas.

Artificially reproducing a mother's milk is a very complicated pursuit because its composition is complex and varies over time, even in the same feeding. Artificial milk comprises of a heterogeneous mixture of components derived from cow, goat or soy milk with different degrees of hydrolysis that provide energy, proteins, fats, and carbohydrates, to which minerals and vitamins are generally added. Infant formulas are usually classified into three types, beginning, continuation and growth, the composition of the first two being regulated by European regulations [1].

We propose using spirulina, hailed by the World Health Organization (WHO) as the best food for the future at the 1974 United Nations World Food Conference, in infant formulas. Spirulina is the most complete food and has great similarities with breast milk, it is rich in iron, proteins, and vitamins and can be administered to children without any risk [2]. Proof of its interest was the creation of the United Nations agency Intergovernmental Institution for the use of Microalgae Spirulina Against Malnutrition (IIMSAM) [3] with the mission of a world free of hunger and malnutrition. This organization, sadly, seems to have not met its objectives [4].

Additionally, we suggest including the Schizochytrium sp. in the formulation [5]. This microalgae is a powerful source of lipids, mainly docosahexaenoic acid (DHA) that will enhance the proposed formula, making it even richer and more similar to breast milk in composition.

BREAST MILK COMPOSITION AND BENEFITS.

Breast milk is a baby's healthiest option because it contains all the essential nutrients they need, and it has long been known that breastfeeding is good for both mom and baby (6). The composition of breast milk changes over time [7]. The first one is colostrum, a yellowish milk with high density, and its volume increases up to 100 ml with the intensity and frequency of the sucking stimulus. Colostrum has 87% water; 2.9g/100 ml. of fat; 5.5g/100ml of lactose and 2.3g/100 ml. of proteins providing 58 Kcal/100 ml. The concentration of IgA and lactoferrin, along with the high number of lymphocytes and macrophages, confers a protective condition for the newborn. Next is transition milk, between the fourth and tenth day postpartum and a volume from 400 to 600 ml/day, with an increase in the content of lactose, fats, calories and water-soluble vitamins and decreases in proteins, immunoglobulins and fat-soluble vitamins. From the tenth day onwards, mature milk is produced with an average daily volume of 700 to 800 ml/day.

Mature milk components are:

Water: Water represents approximately 88 to 90%. It is very important to maintain hydration and it is the medium where all the nutrients are found.

Carbohydrates: 7.3 grams/100 ml of the total components of milk. The main sugar is lactose, with a fundamental osmotic value to maintain its density. In addition, there are more than 50 oligosaccharides that make up 1.2% of milk, including: glucose, galactose and others. All these carbohydrates and glycoproteins have a beneficial effect on the development of lactobacillus bifidus.

Lipids: Varies from 3 to 4 grams/100 ml of milk constituents. It is the component with the greatest variations in concentration during lactation. Provides 30 to 55% of kilocalories. The largest component is triglycerides, but it also contains phospholipids, cholesterol, and polyunsaturated fatty acids, including linoleic acid and docosahexaenoic acid, with a primary effect on the development of the central nervous system.

Proteins: 1 g/100 ml., constitutes 0.9% of the milk, the highest percentage corresponds to casein (40%) and the remaining 60% to whey proteins: lysozyme, lactalbumin, lactoferrin that contributes to the absorption of iron in the child's intestine and fixes it, preventing it from being used by bacteria. Furthermore, as part of non-protein Nitrogen, free amino acids are found, among them the powerful neurotransmitter taurine, which the newborn is not able to synthesize. The presence of immunoglobulins is noteworthy. IgA, IgG, IgM.

Vitamins: Human milk contains all vitamins. Given that their vitamin K concentration is low, every newborn should receive a preventive dose intramuscularly at birth. There are variations in water-soluble vitamins, and they depend on the mother's diet.

Minerals and trace elements: The quantities found are sufficient for the needs of the infant, including iron, zinc, calcium, phosphorus and selenium among others.

Difficulties in replicating breast milk: Why cow's milk and others are not ideal substitutes The immature gastrointestinal tract of newborns is highly permeable, delaying the production of protective antibodies and increasing susceptibility to allergies from cow's milk proteins. Cow's milk has been linked to various issues including gastroenteropathy, dermatitis, respiratory problems, and even failure to thrive. Moreover, cow's milk forms clots in the stomach, slowing gastric emptying, unlike human milk which is easily digestible due to its softer casein structure [8]. Additionally, cow's milk has higher osmolarity, taxing kidneys more than human milk. Immunologically, human milk provides antibodies (IgA) for protection, whereas cow's milk contains beta lactoglobulin associated with allergic reactions. Gastric emptying for human milk is faster (90 minutes) compared

to cow's milk (3 hours), affecting feeding frequency and digestion.

PROPOSAL: MICROALGAE-ENRICHED FORMULA

Enhancing artificial infant formula with Spirulina and Shizochytrium sp. for optimal nutrition: Microalgae are an old sustainable food with a lot of nutraceuticals, and spirulina deserve the title of "the food of future". Microalgae has a disruptive potential for food application for its health benefits. [9-12].

Spirulina is a living organism that has been consumed as food for centuries, including by pregnant women in Mexico, where it was known as *Tecuitlatl* by the Aztecs, and by the Kanembu people in Africa, who referred to it as *Dihé*. It contains most of the elements described in human milk [13]. Spirulina has no cellulose in its cell walls, composed of soft mucopolysaccharides making it easily assimilated - 85 to 95% digestible (this is important for infants and people with intestinal malabsorption).

Spirulina contains 15 to 25% carbohydrate and sugar. The primary forms are rhamnose and glycogen, two polysaccharides which are easily absorbed by the body. Spirulina offers quick energy, without taxing the pancreas or precipitating hypoglycemia.

Spirulina has 4 to 7% lipids or fats, and most are essential fatty acids (EFA). About 20 to 25% of the lipids of spirulina is gamma-linolenic acid (GLA). The only other known sources of dietary GLA are mother's milk and extracts of evening primrose, black currant and borage seeds. Others included are linoleic and oleic acid. Three classes of lipids in spirulina are called neutral lipids, glycolipids and phospholipids. Glycolipids are 40% of the lipids and contain sulfolipids from 2-5% of the total lipids. Furthermore, supplementation with the algae Schizochytrium sp., known for its richness in lipids, would provide the essential fats needed to complement those naturally found in breast milk [14].

Spirulina (Arthrospira platensis and Arthrospira maxima) is considered as GRAS (Generally Recognized as Safe) and can be used for its safety in dietary supplements into The United States Pharmacopeia Convention - National Formulary (USP - NF). [15]

Table 1. Below table summarizes the key components of spirulina and their respective benefits to the organism, adjusted to Recommended Daily Allowance (RDA of children before 6 years old). [16]

Component	Content in 10 g Spirulina	%RDA Children	Effects on organism
Minerals			
Calcium	100 mg	12%	Supports bone health and various enzymatic processes.
Iron	18 mg	128%	Aids in the recovery of iron levels, especially in children.
Phosphorus	80 mg	11%	Vital for energy production and bone formation.
Potassium	280 mg	7%	Helps maintain normal cell function and regulates fluid balance.
Magnesium	40 mg	34%	Important for muscle and nerve function, and energy production.
Manganese	0,5 mg	25%	Supports metabolism and antioxidant defense.
Chromium	28 mcg	61%	Enhances insulin action and glucose metabolism.
Selenium	2 mcg	4%	Acts as an antioxidant, protecting cells from damage.
Copper	78 mcg	6%	Essential for iron metabolism and the formation of red blood cells.
Zinc	0,3 mg	3%	Aids in immune function, wound healing, and protein synthesis; effective in curing zinc deficiency in children.
Vitamins			
Vitamin A (beta-carotene)	14 mg	1400%	Supports vision, immune function, and skin health.
Thiamine (B1)	0,35 mg	50%	Important for energy metabolism and nerve function.
Riboflavin (B2)	0,4 mg	50%	Essential for energy production and cellular function.
Niacin (B3)	1,4 mg	16%	Supports metabolism and skin health.
Pantothenic Acid (B5)	0,01 mg	0,5%	Important for synthesizing coenzyme A, essential in fatty acid metabolism.

Component	Content in 10 g Spirulina	%RDA Children	Effects on organism
Pyridoxine (B6)	0,06 mg	7%	Vital for amino acid metabolism and neurotransmitter synthesis.
Folic Acid (B9)	0,01 mg	10%	Important for DNA synthesis and repair.
Cyanocobalamin (B12)	3,2 mcg	280%	Essential for red blood cell formation and neurological function.
Alpha-tocopherol (E)	1 mg	20%	Acts as an antioxidant, protecting cells from damage.
Vitamin K	244 mcg	325%	Promotes coagulation, fights against cellular aging
Amino Acids			
Essential Amino Acids	All of them	58% (30-140)	Provides complete protein profile with high Net Protein Utilization (NPU).
Nonessential Amino Acids	9	-	Supports various physiological processes and tissue repair.
Other Components			
Phycocyanin	1,800-2,200 mg	-	Exhibits antioxidant, anti-inflammatory, immune-modulatory, and anti-cancer activities.
Superoxide Dismutase (SOD)	10-35.000 UI	-	Quenches free radicals and retards aging.
Chlorophyll	79 mg	-	Promotes healing, natural antiseptic, fights anemia

Humans need essential minerals and trace minerals for the functioning of enzyme systems and other physiological functions. Ten grams of spirulina supply an interesting Dietary Value (DV) in calcium (12%), iron (128%), phosphorus (11%), potassium (7%), magnesium (11%), manganese (25%), chromium (21%), selenium (4%), copper (6%) and zinc (2%). An important key is that they are bound to organic substances and their absorption by the body is much greater than when organic mineral substances are used [17].

Spirulina can be more effective as a zinc supplement in curing zinc deficiency in children (1994). The effective dose of zinc from spirulina was 2 to 4 times less than the zinc from a common supplement, zinc sulfate. With 100 children with zinc deficiency, in a three-month period, 50 children were given zinc sulfate and 50 were given spirulina tablets. Doctors concluded spirulina's effect was much better than zinc sulfate, had no side effects and was easy to administer for long periods of time [18].

Spirulina is very useful for recovering iron levels. This 2022 double-blind research in Cambodia uses spirulina at a dose of 2 g/day for 50 days with children between 4 and 7 years of age. The improvement is significant [19].

Regarding vitamins, spirulina has vitamin A in form of beta carotene, thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B8), folic acid (B9), cyanocobalamin (B12), alpha-tocopherol (E), inositol, and vitamin K. It does not contain vitamin C and D.

A study in China, with 30 children (6-11 years) with a placebo group, confirms that spirulina taken for 10 weeks is a safe and good dietary source of beta-carotene and vitamin A [20]. Total-body vitamin A stores increased significantly, with a median increase of 0·160 mmol in children taking 2 g spirulina and of 0·279 mmol in children taking 4 g spirulina. No adverse effects were observed.

Another study with 400 healthy school children (3-5 years) and control group, a daily dose of beta-carotene from 2 g spirulina during 30 days increased the children's vitamin A status to the same level as those administered pure vitamin A [21]. There was no appreciable change in the weight after supplementation.

Spirulina contains approximately 60% protein, with a 10g dose providing significant amounts of all essential amino acids: phenylalanine (110%), histidine (20%), isoleucine (50%), leucine (55%), lysine (36%), methionine

(70%), threonine (64%), tryptophan (36%), and valine (50%). It also contains nonessential amino acids including alanine, arginine, aspartic acid, cysteine, glutamic acid, glycine, proline, serine and tyrosine. On the other hand, proteins in spirulina have a high Net Protein Utilization (NPU), and multiplying protein quantity by the NPU, we can determine usable protein as a percentage of the food's composition. Spirulina is second only to dried eggs, and higher than any common foods in the form they are usually purchased.

Spirulina contains several enzymes, one of which, Superoxide dismutase (SOD), is important in quenching free radicals and in retarding aging.

An important component of spirulina is phycocyanin, (18-22% in weight) a blue-red fluorescent, water-soluble and non-toxic biliprotein pigment. It is reported to be the main active ingredient of Arthrospira and was shown to have therapeutic properties, including antioxidant, anti-inflammatory, immune-modulatory and anti-cancer activities [22].

Docosahexaenoic acid (DHA), an essential n-3 long-chain polyunsaturated fatty acid (LCPUFA) should be added to infant and follow-on formula in Europe. A study in infants aged 5-6 months in Japan, cow's milk formula (CMF) supplemented with 15.9% linolenic acid, 1.6% α-linolenic acid, 0.40% DHA, and 0.27% arachidonic acid was used. Significant positive associations with infants' serum DHA levels were found [23]. Due to its structure, it has a role in the nervous system and the retina and its involvement in normal brain and visual development.

GUT-BRAIN AXIS AND INFANT DEVELOPMENT.

Role of bacterial flora in infant digestion: Just after birth, the colonization of the intestines by the microbiota begins rapidly after months of protection in the maternal uterus. There is evidence that there is a close relationship between the intestinal microbiota and human health.

Appropriate nutrition in the first stages of life is crucial for the individual because it is the time when the first contact with the outside world is made and the recognition system is configured and developed at the brain level, including the immune system, and of course the gastrointestinal health in food management and its absorption of his components. The infant's intestine is colonized in its first moments by Bifidobacterium because they are the ones who consume oligosaccharides contained in breast milk and their diversity increases when milk intake decreases in favor of solid foods. At three years old, the microbiome of an adult is reached.

Intestinal microbiota is essential in the organization of the immune system since there are between 1,000 and 1,500 different species of bacteria, also microbiota is capable of metabolizing glutamate and synthesizing gamma amino butyric acid (GABA) or serotonin, fundamental neurotransmitters of the central nervous system. Based on this theory, the microbiota intervenes in the development, physiology and cognitive functions of the brain.

It is recognized that the type of microbiota of the individual depends mainly on the food consumed. Prebiotics in the diet are beneficial for creating a favorable environment for the growth of microorganisms. Among these are polysaccharides and oligosaccharides, which are not broken down in the stomach or small intestine and reach the large intestine intact, where they are fermented by bacteria. Breast milk contains 6-7% lactose, 3-4% lipids as a source of energy, and oligosaccharides, which represent 10-15% of the total solids content of milk. These oligosaccharides vary depending on the maternal diet and the stage of lactation, and not only promote the healthy growth of

the bacterial flora but also play a role in the defense process against pathogens by preventing their adhesion to epithelial cells.

The prebiotic effect of Spirulina algae is due to its composition rich in complex oligosaccharides, which its consumption can promote the growth of intestinal microflora, specially stimulating the growth of Bacteroides, Escherichia-Shigella, Megamonas, Megasphaera, Blautia, Bifidobacterium and Lactobacillus. In addition, by maintaining intestinal homeostasis, oligosaccharides promote the development of beneficial microbes, defend the microbiota against pathogens, and protect gastrointestinal function and immunoregulation through the increase in immunoglobulin A [24, 25].

In Japan, a study showed spirulina increased lactobacillus in rats 3 times over a control group. A diet with 5% spirulina for 100 days showed 1) caecum weight up 13%, 2) lactobacillus up 327%, and 3) Vitamin B1 inside the caecum up 43%. Since spirulina did not supply additional B1, it improved B1 absorption. It should increase lactobacillus in humans and raise the absorption of vitamins [26].

Spirulina promoted high proliferation of Lactobacillus acidophilus in culture medium and differently modulate the intestinal microbiota of medium-age healthy individuals through an in vitro gut microbiome model [27].

Likewise, the microbiota has a dynamic and bidirectional interaction with the central nervous system (CNS), through the microbiota-gut-brain axis [28].

Lactic acid bacteria can be included in infant formulas or used in pre-treatment of infant formula milk to improve its nutritional value and safety [29].

A recent study, a placebo controlled double blinded randomized controlled trial of 36 twin pairs of aged people show that gut microbiota may play a role in both anabolic resistance of older muscle, and cognition [30].

Brain health connection (gut-brain axis in cognitive development): Infancy is a key for brain development; it is particularly rapid in the first years of life and requires nurturing care, such as suitable nutrition. Myelin is an insulating layer, or sheath that forms around nerves, allowing electrical impulses to transmit quickly and efficiently, in this case, along the neurons. In humans, myelination begins in the fifth fetal month, and the brain is almost completely myelinated by the end of the second year of life. Myelin deposition appeared to be almost solely responsible for the continued increase in brain weight [31]. If myelin is damaged, these impulses slow down. Myelination is the process where human neurodevelopment ensuring coordinated communication between brain cells and networks. It is accepted that higher nutrient intakes are associated with higher measures of brain myelin and brain growth.

Today it is possible to study the developmental dynamics of nutrient-myelin interactions from infancy to early childhood using myelin imaging as a marker for brain structural maturation. A recent study identified, in 293 healthy children, 3 nutrient-myelin windows covering the age range of 1–5 years: the window from 6 to 20 months there is 60% positive nutrient correlations, window 2 from 20 to 30 months with 20% positive correlations, and window 3 from 30 to 60 months with 37% positive correlations. After 2.5 years of age myelin increase continues at a slower rate [32].

This window from 6 to 30 months is a time of great cognitive, emotional and social development including not only an increase in brain and body size, but fine and gross control of muscles which enable walking or manipulate objects, vision and retina development to interact with the world with the aid of hearing

understand and learn language and speech to communicate effectively.

The formation of the myelin sheath requires high levels of fatty acid and lipid synthesis as well as the uptake of extracellular fatty acids as docosahexaenoic acid (DHA), arachidonic acid (ARA), amino acids (isoleucine, leucine, lysine, phenylalanine, proline, serine, threonine, tyrosine and valine), micronutrients and minerals (cooper, iron, magnesium, phosphorus, potassium, selenium, zinc and sodium), vitamins (folic acid and analogues, vitamin A, vitamin B1, vitamin B2, vitamins B6, vitamin B12).

Behavioral development is related to cognitive and brain development and the most profound changes occur during childhood, and as the child grows older, developmental trajectories tend to become more stable. What happens during the first 3 years of life may be foundational for later cognitive and learning outcomes, including the IQ (Intelligence Quotient) [33].

A recent randomized, double-blind, controlled clinical trial have been carried out where infants have been supplemented with phospholipids and long chain polyunsaturated fatty acids and its effects on growth parameters and neurodevelopmental outcomes [34]. Notably, the test scores of infants fed the investigational formula were similar to those who were breastfed and may be beneficial for neurodevelopment of infants throughout the first year of life.

Also, a double-blind, randomized, controlled, parallel group research from Nestle, concluded that a 12-month supplementation with a blend of DHA, ARA, iron, vitamin B12, folic acid, and sphingomyelin from a uniquely processed whey protein concentrate enriched in alpha-lactalbumin and phospholipids in neurotypical well-nourished term infants increases myelination over the first 2 years of life. Significant differences in myelin structure, volume, and rate of myelination were observed in favor of the investigational myelin blend at 3 and 6 months of life. Effects were demonstrated for whole brain myelin and for cerebellar, parietal, occipital, and temporal regions, known to be functionally involved in sensory, motor, and language skills [35].

Spirulina regulates the expression of the neurotrophic factor (BDNF Brain-Derived Neurotrophic Factor) [36]. BDNF is a member of the family of neurotrophic factors, which are proteins that promote the growth and survival of neurons. Its main function is to promote neuronal survival, stimulate the growth of new neurons (neurogenesis), and promote synaptic plasticity, which is the brain's ability to change and adapt in response to experience and learning. Early childhood is the period where synaptic pruning occurs, and most neural networks are formed.

On the other hand, it has been observed that spirulina, and more specifically the phycocyanin it contains, reduces the progression in cases of multiple sclerosis by controlling neuroinflammation and the processes of creation and destruction of myelin in neurons [37]. Also spirulina could be considered a potential natural drug to prevention and/or prevention of neurodegenerative diseases, in particular Parkinson, Alzheimer or Multiple Sclerosis [38].

Dietary administration of 1% and 2% Spirulina platensis for 16 weeks significantly improved the spatial learning and memory performance of the High Fat Diet mice in both Barnes Maze test and Morris water maze test. The Aβ accumulation, tau-hyperphosphorylation, and neuroinflammation in the hippocampus were significantly inhibited by Spirulina. Spirulina also abrogated HFD induced gut microbial dysbiosis and unbalance of gut microbial metabolites indicating its modulating effect on the gut microbiome-brain axis [39].

In this review article, spirulina acts as a potent protein source and neuroprotectant against protein

malnutrition (PMN) induced deleterious changes [40]. Also, it discusses its immunomodulatory properties, which support the adaptation of the baby's immune system to changing environmental conditions and enhance immunity against infectious diseases, particularly those arising from malnutrition.

After protein malnutrition (PMN), cellular changes in the hippocampus are partially restored after maternal spirulina protein supplementation [41]. In addition, it reduced the astrocytes and activation of microglia, and increased cerebral cortical thickness, which is a better morphology of neuronal cells. They investigate the effects of breastfeeding milk with spirulina supplementation against PMN-induced oxidative stress, reactive gliosis and neuronal damage in the hippocampus of F1 progeny. Spirulina consumption partially prevented or attenuated oxidative brain damage, reduced reactive gliosis and apoptotic cell population, improved dendritic branch complexity with few damaged neurons and enhanced mushroom-shaped spine density.

Review of key studies on microalgae in infant nutrition: Spirulina, which is naturally found in the alkaline lakes of North Africa and Mexico, has consumed by humans since ancient times. Although its nutritional properties were recognized in the mid-20th century, many studies, especially involving children in malnutrition-affected areas, have limitations such as the absence of control groups or double-blind methodologies [42]. Spirulina has been shown to support not only nutritional status but also cognitive and motor development. It has beneficial effects on language acquisition and locomotion in children.

Table 2. This table summarizes the key components of spirulina and their respective benefits to the organism.

Year	Location	Study Population	Spirulina Dosage	Results / Observations	Reference
1973	Mexico	Malnourished infants and children	Up to 15 g/day	Complete recovery in severe cases, no side effects observed	[43]
1975	France	Malnourished Aged men	Up to 90 g/day	Recovery, and no side effects	[44]
1985	Togo	Infants with Kwashiorkor and Marasmus	3-15 g/day	Full recovery after 3 months of treatment	[45]
1987	China	27 children, 2-6 years old	1.5g spirulina, barley vit B1 and zinc	Recovered in a short period from bad appetite, night sweats, diarrhea and constipation	[46]
1990	Angola	28 severely malnourished children	10 g/day	Improved health markers and albumin levels	[47]
1991	India	5000 preschool-age children	1 g/day for ≥150 days	Bitot's spots decreased from 80% to 10 %	[48]
1993	Belarus	Children post-Chernobyl disaster	5 g/day for 20 days	50% reduction in urine radioactivity levels	[49]
1995	India	60 children (1-6 years)	1 g/day during 3 months	Significant increase in serum protein, hemoglobin, ferritin, and vitamin A	[50]
1999	Senegal	malnourished children	10 g/day for 60 days	Significant increase in all hemoglobin, albumin and weight values	[51]
2003	Burkina Faso	182 malnourished children (3 months - 3 years)	5 g/day	No additional benefit observed compared to traditional renutrition	[52]
2003	Niger	56 malnourished children	10g/day for 2 weeks	Weight, albumin and prealbumin values increased significantly	[53]
2004	India	60 school-age girls (7-9 years	1 g/day for 2 months	Improvement of the hematological profile intellectual performance	[54]
2005	Burkina Faso	170 malnourished children <5 years	10 g/day	Anemia decreased in all children	[55]
2006	Burkina Faso	550 malnourished children	Spirulina is compared to misola	Correct weight loss in a shorter period	[56]
2009	Senegal	young children (7-year-old media)	2g/day and 10 g of honey, 2 months	Academic performance was improved	[57]
2016	Gaza Strip	Malnourished children	10 g/day	Increased ferritin and iron levels; effective against malnutrition	[17]
2016	Congo	50 malnourished children, aged between 0.5 and 60 months	10 g/day for 30 days	A rapid and significant improvement was observed	[58]
2017	Niger	twin brothers, 6 months and 15 years old with Sickle cell disease	5 g/day of spirulina for 9 months	An appreciable decrease in the number of pain crises	[59]
2019	Zambia	501 children (18-30 months)	10 g/day	Improvement in growth, motor skills, and lower morbidity	[60]
2021	Kenya	Iron deficient in children aged 6-23 months	Spirulina corn soy blend	The probabilities of survival increased significantly	[61]

Year	Location	Study Population	Spirulina Dosage	Results / Observations	Reference
2022	India	Children (6 months - 6 years)	5% spirulina in food (Chikki)	Improved nutritional status (weight, height, arm circumference)	[62]
2023	Egypt	General children population	0.5-2% spirulina in food	Enhanced acceptance with spirulina in some foods like frozen yogurt and gelatin	[63]
2024	Ethiopia	Primary school children	Spirulina-enriched bread	Assessing parental willingness to purchase spirulina-enriched products; study evaluating health and nutritional impacts ongoing	[64]

Research Gaps and Limitations: Why has Spirulina not been used in children's nutrition? There has been a noticeable lack of recent research or publications on spirulina and infant nutrition. This year marks the 50th anniversary of the WHO's declaration, when they hailed spirulina as possibly the best food for the future and for mankind, calling it 'a highly credible source'. It was proven that spirulina has the most complete nutritional composition compared to all other plant and animal. Spirulina can be used as a functional foods category [65], in this case in infant formulas or as we suggested, and combined with cocoa, to fight against COVID19 [66].

From the studies shown so far, it can be assured that spirulina is suitable for the treatment and prevention of malnutrition, especially in children, but only a study in 2014 talks about the use of spirulina in complementary baby foods. They used spirulina at different concentrations (0.25%, 0.5%, and 7.5%) in two types of food formulations: fruits and vegetables, or cereals and legumes. All formulas were found to be sensory acceptable and microbiologically safe [67].

Quality of spirulina and possible contamination by heavy metals and other cyanobacteria: Spirulina is a cyanobacteria, and there are certain other aquatic bloom-forming cyanobacterias that produce cyanotoxins, such as Microcystis, Oscillatoria, Anabaena, and Nostoc. These toxins are classified according to the mode of action, into Hepatotoxins (Microcystins), Neurotoxins (Anatoxins), skin irritants and others. Microcystins is a hepatotoxin with acute health effects on humans causing hemorrhagic shock.

To date, Spirulina is considered a non-toxin-producing cyanobacterium, also the United States Pharmacopeia (USP) and the National Formulary (NF) unanimously voted for a Class A safety assignment for S. maxima and S. platensis, indicating that the available evidence does not indicate a serious risk to health or other public health concern when these dietary ingredients are properly identified, formulated, and used. [14]. It is unlikely for toxic cyanobacteria to contaminate spirulina ponds when it is cultivated in closed ponds or phobioreactors due its high salt concentration (30g/l) and PH >11. [68,69]

A study of 95 French spirulina producers, using 623 dry spirulina samples and 105 spirulina culture samples between 2013 and 2021, confirmed that French spirulina production remained within safe regulatory levels for microcystin contamination [70].

In Spirulina strains grown in an uncontrolled and unmonitored environment such as outdoor ponds or lakes, cyanotoxin contamination is of serious concern. There are studies regarding microbial population of commercially available spirulina products including for the presence of cyanobacterial toxins. Microcystin toxins were detected in all the products at levels that could lead to consumers exceeding their recommended daily limits, which indicates that industrial ponds sometimes become contaminated with toxic cyanobacteria species [71].

Other studies on spirulina dietary products from different countries found no detection of microcystin-producing cyanobacteria [72-74]. Spirulina also acts against microcystins. According to this study, spirulina alleviated microcystin-induced organ toxicities by mitigating oxidative and nitrosative stress and lipid peroxidation [75].

Heavy metals are a separate issue, since spirulina can metabolize them. For example, spirulina can be

enriched with selenium simply by adding a selenium salt to the culture, and the same method can be applied to other metals. Because of this ability, spirulina is used to decontaminate soils and to help eliminate heavy metals from the body. This study reveals the concentrations of six typical heavy metals/minerals (Ni, Zn, Hg, Pt, Mg, and Mn) in 25 Spirulina products commercialized were not found to exceed the present regulation levels, and thus can be considered as safe food [76].

Spirulina is a food and, like any other, must comply with the appropriate controls and meet all necessary requirements for safe consumption, especially when it comes to children. Nevertheless, public standards are essential for obtaining a safe spirulina product and the risk posed by cyanotoxins should not be underestimated, as they can be detrimental to human health. Here are the food safety quality standards for spirulina as outlined by the Food and Agriculture Organization (FAO) [77]. We need continuous monitoring not only for heavy metals and mycotoxins, but also antibiotics, nitrate, and even polycyclic aromatic hydrocarbon levels [78].

Finally, we want to mention that it is very necessary to monitor phycocyanin content. The elimination of this is a simple and lucrative process, which reduces its health properties, but with a simple spectrophotometer it is easy to know its concentration [79].

CONCLUSION AND RECOMMENDATIONS:

Breast milk substitute complementary feeding is the process that begins when breast milk or infant formula alone is no longer sufficient to meet the nutritional requirements of infants, necessitating the introduction of other foods and liquids alongside human milk or a breast milk substitute. In this context, the addition of microalgae products is recommended.

As a preventive measure and to replicate breast milk formulation as closely as possible, it is advisable to periodically add a small amount of spirulina to children's milk formula. The recommended amounts are 1/2 teaspoon for ages 0 to 2 years and 1 teaspoon thereafter, with 1 teaspoon equivalent to 5 grams. This translates to 2-3 grams of spirulina for children aged 0 to 2 years and 5-10 grams for those older than 2 years. In addition to its nutritional properties, this supplementation will help infants enhance their disease resistance and support growth.

Spirulina is not a drug, but a natural food supplement, and is not habit forming. Its effects can be sustained by taking it regularly at approximately 2 to 5 g/day. To see any benefits of spirulina, it should be taken for at least 6-8 weeks.

The DHA supplement at a dose of 250 mg/day was effective in increasing serum DHA and can be provided by Schizochytrium sp.

In conclusion, the incorporation of microalgae, specifically Spirulina and Schizochytrium, into infant nutrition holds significant promise for enhancing the health and development of newborns. These microalgae offer a wealth of essential nutrients, such as proteins, vitamins, minerals, and omega-3 fatty acids, which are vital for supporting early growth, brain maturation, immune system function, and overall well-being in neonates. Studies have illustrated the positive effects of introducing Spirulina into diets, leading to improvements in nutritional status and individual health outcomes in newborns.

Moreover, the similarities between Spirulina and the composition of breast milk underscore their potential as valuable components in newborn formulas, providing immunological, antioxidant, and neuroprotective benefits that can help prevent nutritional deficiencies and promote healthy development. While opinions may vary regarding the widespread use of Spirulina for addressing malnutrition in newborns, the evidence presented emphasizes the potential of microalgae supplementation in bolstering infant nutrition and

supporting optimal growth during the crucial early stages of life.

By recognizing the nutritional advantages and bioactive properties of microalgae, and their ability to replicate the benefits of breast milk, the proposal to enrich newborn formulas with Spirulina and Schizochytrium emerges as a promising strategy to meet the specific nutritional requirements of newborns, enhance their immune defenses and contribute to their overall health and well-being in the critical neonatal period.

In Memoriam: Ripley D. Fox (1920-2012) & Jean-Paul Jourdan (1930-2023), Pioneers of Spirulina, Hope for A Hungry World.

List of Abbreviations: BDNF: Brain-Derived Neurotrophic Factor; CNS: Central Nervous System; EFA: Essential fatty acids; DHA: Docosahexaenoic acid; GLA: Gamma-linolenic acid; GRAS: Generally Recognized As Safe; DV: Dietary Value; NPU: Net Protein Utilization; SOD: Superoxide dismutase; WHO: World Health Organization.

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