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Review Article

Exploring micronutrient supplements in disease conditions: are they effective?

Running title: Micronutrient supplements in disease conditions

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Highlights

The deficiency of micronutrients predisposes to disease and exacerbates it.
The supplementation of micronutrient improves health outcomes.
Micronutrients can alleviate communicable and non-communicable diseases.

Abstract: Nutrition is essential for the health and well-being of all living beings and is sourced from foods of different origins and types. Most importantly, the food must contain carbohydrates, proteins, fat, vitamins and minerals in a balanced form to achieve optimum benefits. Vitamins and minerals, also known as micronutrients, are characterised by their nature, quantity and role in normal metabolic activities. In humans, micronutrients are exclusively obtained from food or supplements. In addition, vitamin D3 is synthesized de novo with the aid of sunlight, while vitamins B and K are synthesized in the gut by the resident bacteria. Micronutrients play an important role in health and disease states and have become the most widely used dietary supplements in the world. However, how effective they are against diseases is controversial as conflicting reports continue to emerge, especially where insufficient data is available. This review highlights the important role of micronutrient supplements in the alleviation of communicable and non-communicable diseases. Data were retrieved from the literature in databases including African Journal Online, Google Scholar, PubMed and Web of Science, among others, with hits on nutrients, vitamins and mineral supplements: Only literature with relevant information from 1993-2023 (30 years) was considered. As important as these micronutrients are for health and their supplementations are generally beneficial, it is worthy of note that their role in the disease treatment is still limited by insufficient data.

Keywords: Vitamins, Minerals, Supplementation, Health, Diseases

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Introduction

Humans and nutrition are inextricably linked, as the former depends on the latter for proper well-being and development [1]. Nutrition is vital for all ages of humans, but children, pregnant women and lactating mothers tend to be more vulnerable, as it is required to support developmental and metabolic processes and strengthen the immune system, thereby reducing the risk of contracting diseases and prolonging longevity [1, 2]. Generally, food serves as the main source of human nutrition. However, for food to play this role effectively, it must contain the basic nutrients, including proteins, carbohydrates, fat, minerals and vitamins [2]. However, these nutrients are not present in sufficient quantities or proportions in foods. This leads to malnutrition and thus to a variety of adverse health problems and poor developmental processes [3-7].

Two very important nutritional components are vitamins and minerals [2]. As these are highly effective, they are only needed in minute quantities and so-called micronutrients [3]. These micronutrients are essential for the normal metabolic activities of the body and are mainly obtained from fruits, vegetables and nuts, as well as dairy products, seafood, poultry, meat, fortified processed products and supplements [8-12]. While some vitamins can be produced in the human body directly or indirectly by gut bacteria, minerals must be obtained from food or supplements [13-16]. These dietary supplements provide concentrated micronutrients that are needed by some individuals whose normal dietary intake is not sufficient and can also target conditional-induced deficiencies [11, 12, 14].

Dietary micronutrient deficiency is a global public health problem that is not limited to gender or age, but is more prevalent in children and pregnant women and in low-income countries [2, 5, 6, 11]. Although micronutrient deficiency is a global problem and tends to affect certain regions more, either due to cultural preferences, type of diet, or economic status [2, 6, 7]. Insufficient nutrient intake is the main cause due to more consumption of processed foods, demineralized water and agricultural practices that use mineral-deficient soil to grow food [14]. These and other reasons have led to an increase in the use of dietary supplements [2, 9, 12, 13]. As important as these micronutrient supplements are for supporting health and combating diseases [3, 14, 15], can they also help protect against diseases or their pathogens? The literature on this topic is far from exhaustive. Recent reviews have shown the positive roles of various micronutrient supplements in the treatment of viral diseases [17-20], but there are few original studies whose protection against or reversal of the viral conditions is unconvincing. There is a lack of up-to-date information on bacterial and other pathogens, as well as non-communicable diseases. This review highlights the important role of micronutrient supplements in alleviating communicable and non-communicable diseases.

Literature search

About five hundred articles were searched for empirical data and reviews with keywords such as nutrition, vitamins, minerals, micronutrients, supplementation and diseases. These were obtained from journals and books whose full-text contents were relevant. The period covered was from 1993-2023 (30 years). The following databases were accessed in chronological order: African Journals Online (AJOL), Cochrane Library, Directory of Open Access Journals (DOAJ), Google Scholar, Medical Literature Analysis and Retrieval System Online (MLARSO), National Diet Library Collection (NDLC), Scientific Information Database (SID), Science Direct, Scopus, and Web of Science (WOS) (Figure 1).

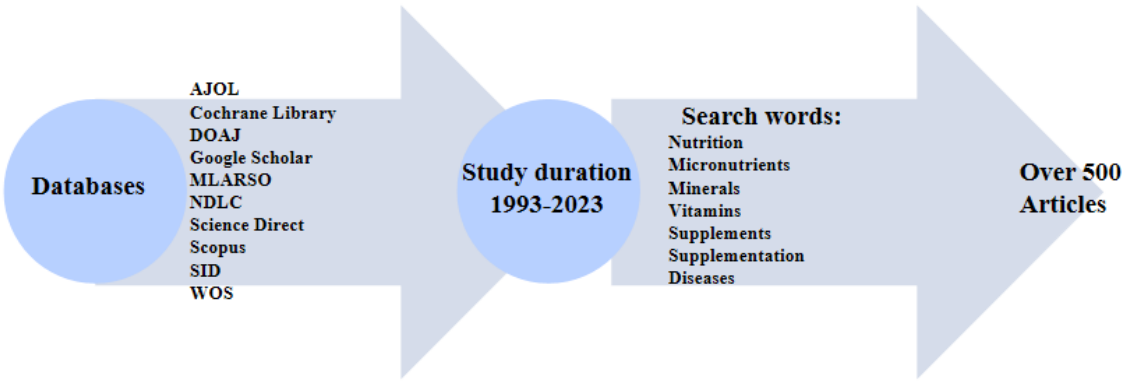

Figure 1. Searched databases, relevant information and number of articles considered

Classification of micronutrients

Micronutrients are in two forms: vitamins and minerals [2, 3, 10]. Vitamins are a group of organic substances designated as A, B, C, D, E, and K. Of these vitamins, A, D, E and K are generally classified as fat-soluble, while B and C are classified as water-soluble [3, 16]. Functionally, vitamins A, C and E are considered as major non-enzymatic antioxidants known to protect against oxidative stress associated with several metabolic disorders [2, 3, 8].

Vitamins can also be classified according to whether or not they are synthesised by humans: vitamin D (D3, cholecalciferol) is the only vitamin that is synthesised de novo, although it can also be obtained from food [13, 14, 16]. Other vitamins cannot be synthesised by humans, but are obtained as food produce of plants and animals. These include vitamins A, B, C, E and K. Vitamin B is considered as a complex and is divided into B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate) and B12 (cobalamin) [3, 5, 12, 14].

Minerals are chemical elements that are essential for health [2, 14, 15]. They are generally classified into major and trace minerals: major minerals include calcium, chloride, magnesium, phosphorus, potassium, sodium and sulphur, while trace minerals include boron, chromium, cobalt, copper, fluoride, iodine, iron, manganese, molybdenum, selenium and zinc [10, 14, 15].

Health benefits of micronutrients

Micronutrients are available in foods or their supplements in free forms or as complexes with proteins or other elements [14, 15]. The amount and content of micronutrients vary in different food sources. Some are more abundant in fruits and vegetables, while others are more abundant in animal products and processed foods [3, 8, 10, 14].

Vitamins play an important role in recovery from illness [66]. In the human body, the mechanism of absorption, storage and excretion of vitamins depends on the classification [16,67]. The water-soluble vitamins usually dissolve in water before being absorbed from the gastrointestinal tract to meet the needs of the cells [67]. They are not stored in the body in significant quantities, as they are generally excreted in the urine [11, 16, 67].

In contrast, the fat-soluble vitamins bind to ingested lipids to facilitate their absorption from the gastrointestinal tract [11, 16]. These vitamins are stored in the body, with vitamin K being an exception [68-70]. Therefore, hypervitaminosis may occur, leading to intoxication [68]. Meanwhile, any condition that affects fat absorption will also affect the absorption of these fat-soluble vitamins [11, 16]. The metabolic pathways of micronutrients are illustrated in Figure 2, while their sources and functions are listed in Tables 1 and Table 2.

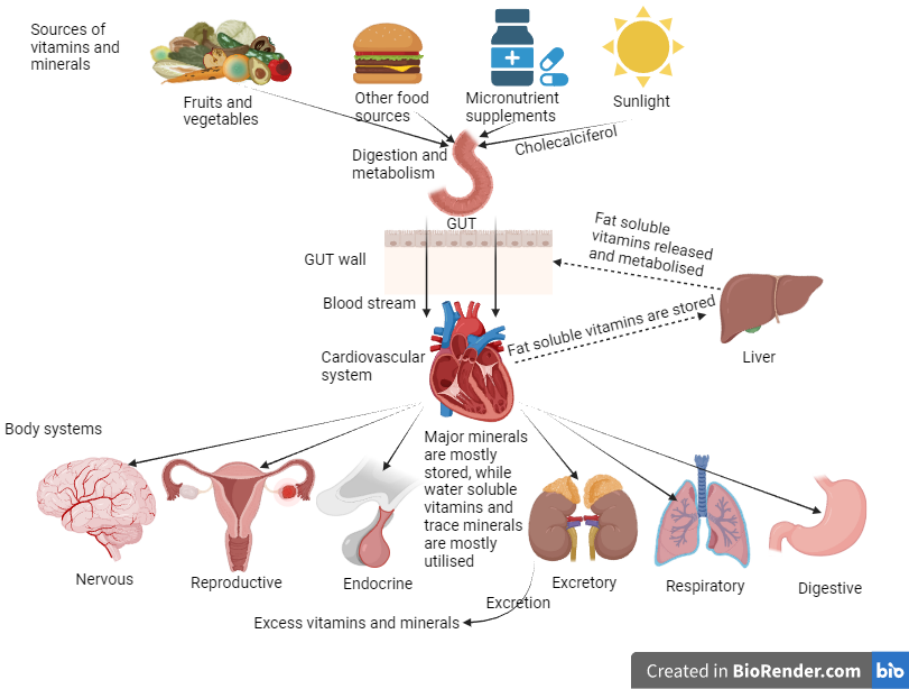

Figure 2. The metabolic pathways of vitamins and minerals

These micronutrients are obtained from various sources, including de novo from sunlight. From their sources, they enter the gut, from where they are either metabolised and absorbed for different body functions or excreted. In most cases, some are stored in the liver and other body tissues and released when needed.

Table 1. Sources and health benefits of vitamins

Vitamins	Recommended daily allowance	Sources	Benefits
A (Retinol)	C<9 - 400 µg C9-18 - 700 µg M<50 - 900 µg M>50 - 900 µg W<50- 700 µg W>50 - 700 mg Wp - 770 µg mg Wl - 1300 µg	Fruit: pawpaw, mango, melon, apricot, grapefruit. Vegetable: carrot, pepper, tomatoes, broccoli, kale. Animal product: cod liver oil, liver, fat, egg. Dairy: milk, cheese, butter.	Growth and development, cognition, as well as immune function and vision maintenance.
B complex B1 (Thiamine)	C<9 - 0.6 mg; C9-18 -1.0 mg; M<50 -1.2 mg; M>50 - 1.2 mg; W<50- 1.1 mg; W>50 - 1.1 mg; Wp - 14 mg; Wl - 14 mg.	Whole grains, legumes, nuts, sunflower seeds, beef, pork, gut bacteria.	B1: Neuronal function, energy production, anti-nociception and cognition.
B2 (Riboflavin)	C<9 - 0.6 mg; C9-18 - 1.0 mg; M<50 - 1.3 mg; M>50 - 1.3 mg; W<50- 1.1 mg; W>50- 1.1 mg; Wp – 1.4 mg; Wl - 1.6 mg.	Leafy green vegetables, whole grains, dairy, eggs, meat, salmon, gut bacteria.	B2: Cellular metabolism, energy production, anti-nociception, regulation of vitamins B1 and B3
B3 (Niacin)	C<9 – 8 mg; C9-18 – 14 mg; M<50 –16 mg; M>50 – 16 mg; W<50- 14 mg; W>50- 14 mg; Wp - 18 mg; Wl - 17 mg.	Leafy green, whole grains, meat, fish, gut bacteria.	B3: Serotonin synthesis
B5 (Pantothenic acid)	C<9 – 3 mg; C9-18 – 5 mg; M<50 –5 mg; M>50 – 5 mg; W<50 - 5 mg; W>50- 5 mg; Wp - 6 mg; Wl - 7 mg.	Chicken, egg yolks, dairy, whole grains, legumes, mushrooms, cabbage, broccoli, gut bacteria.	B5: Coenzyme A (CoA) for metabolism, maintenance of immunological homeostasis
B6 (Pyridoxine)	C<9 – 0.6 mg; C9-18 – 1.2 mg; M<50 –1.3 mg; M>50 – 1.7 mg; W<50- 1.3 mg; W>50- 1.5 mg; Wp - 1.9 mg; Wl - 2 mg;	Poultry, pork, fish, whole grains, legumes, blueberries, gut bacteria.	B6: Cofactor in enzymes; essential in serotonin and γ-amino glutamic acid (GABA) syntheses
B7 (Biotin)	C<9 - 12 µg; C9-18 – 25 µg; M<50 – 30 µg; M>50 – 30 µg; W<50- 30 µg; W>50- 30 µg; Wp - 30 µg; Wl - 35 µg.	Liver, pork, eggs, dairy, banana, sweet potato, nuts, gut bacteria.	B7: Cofactor for acetyl-CoA carboxylase and fatty acid synthase, glucose and amino acid metabolism
B9 (Folate)	C<9 - 200 µg; C9-18 – 400 µg; M<50 – 400 µg; M>50 - 400 µg; W<50- 400 µg; W>50- 400 µg; Wp – 600 µg; Wl - 500 µg.	Citrus, leafy greens, gut bacteria.	B9: Cofactor in several metabolic reactions, DNA, amino acid and monoamine synthesis
B12 (Cobalamin)	C<9 – 1.2 µg; C9-18 – 2.4 µg; M<50 –2.4 µg; M>50 – 2.4 µg; W<50- 2.4 µg; W>50- 2.4 µg; Wp - 2.6 µg; Wl – 2.8 µg.	Dairy, eggs, fish, poultry, meat, gut bacteria	B12: Red blood cell, monoamines and catecholamines syntheses and metabolism
C (Ascorbic acid)	C<9 – 25 mg C9-18 – 65 mg M<50 - 90 mg M>50 - 90 mg W<50- 75mg W>50 -75mg Wp - 85 mg Wl - 120 mg	Fruit: blackcurrant, citrus fruits, strawberry, star apple, guava, kiwi, mango Vegetable: tomatoes, potatoes, pepper, broccoli, brussels sprouts, cauliflower, cabbage.	Syntheses of the monoamines, collagen, carnitine, and bile acid, iron absorption, immune system function, wound healing, cartilage, bones, and teeth maintenance.

D (cholecalciferol)	C<9 - 5 µg C9-18 – 5 µg M<50 - 5 µg M>50 - 10 µg W<50 - 5 µg W>50- 10 µg Wp - 5 µg Wl - 5 µg	Sunlight Dietary sources: cod liver oil, meat, egg yolk, butter, some plants.	Enzymatic and metabolic activities including calcium homeostasis, bone growth, regulation of neuro-development and function, formation and utilization of glutamine, noradrenaline, dopamine and serotonin.
E	C<9 – 7 mg C9-18 – 15 mg M<50 – 15 mg M>50 – 15 mg W<50- 15 mg W>50 - 15 mg Wp - 15 mg Wl - 19 mg	Vegetable oil: palm oil, wheat germ oil, sunflower, almond, peanut and avocado. Fruits: mango, kiwi. Animal products: seafood, poultry, meat.	Antioxidant: inhibits the production of reactive oxygen species molecules, protect cell membrane, regulation of platelet aggregation and protein kinase C activation.
K	C<9 - 55 µg C9-18 – 75 µg M<50 - 120 µg M>50 – 120 µg W<50- 90 µg W>50- 90 µg Wp - 90 µg Wl - 90 µg	Green leafy vegetables, gut bacteria, and chemical synthesis.	γ-glutamyl carboxylase cofactor, coagulation of blood, bone metabolism; neuronal protection and cognition, sperm maturation, intestinal integrity, vascular elasticity, glomerular filtration, beta cell proliferation and insulin production, gut risk microbe suppression, vitamin K dependent proteins activation, promote adipogenesis and anti-inflammation.

C<9 - children < 9 years; C9-18 – children between 9-18 years; M<50 – men < 50 years; M>50 – men > 50 years; W<50- women < 50 years; W>50- women > 50 years; Wp – pregnant women; Wl – lactating women [8, 11, 14, 16, 31, 68, 70, 72, 79, 138-140]

Table 2. Sources and health benefits of minerals

Minerals	Recommended daily allowance	Source	Benefits
Major			
Calcium	C<9 - 600 mg C9-18 - 1,300 mg M<50 - 1,000 mg M>50 - 1,200 mg W<50- 1,000 mg W>50- 1,200 mg Wp - 1,000 mg Wl - 1,000 mg	Dairy: cheese, milk, yogurt, cereals. Fruit: Grapefruit, orange, almonds, sesame chia, kale. Vegetable: spinach, broccoli, okra	Muscle contraction, blood-clotting, bones and teeth formation, and maintenance, neural and synaptic transmission, heart beat and fluid balance regulations
Chloride	C<9 - 1,900 mg C9-18 - 2,300 mg M<50 - 2,300 mg M>50 - 2,000 mg W<50 - 2,300 mg W>50- 2,000 mg Wp - 2,000 mg Wl - 2,000 mg	Dietary salt Vegetables: tomatoes, lettuce, olives, celery, rye; Unprocessed foods: whole grain foods, seafood	Electrolyte and cell homeostasis, action potentials transmitting in neurons, chloride channels trafficking
Magnesium	C<9 - 130 mg C9-18 - 360 mg M<50 - 420 mg M>50 - 420 mg W<50 - 320 mg W>50 - 320 mg Wp - 360 mg Wl - 320 mg	Green vegetables, nuts, seeds, and unprocessed cereals. fruits, fish, meat, and milk products	Cofactor in many enzymatic reactions; neuronal transmission and neuromuscular regulation

Phosphorus	C<9 - 500 mg C9-18 - 1,250 mg M<50 - 700 mg M>50 - 700 mg W<50 - 700 mg W>50 - 700 mg Wp - 700 mg Wl - 700 mg	Dairy: yogurt, milk, cheese Animal products: meats, poultry, fish, eggs Grain products: brown rice, oatmeal Nuts and seeds: cashews sesame seeds Legumes: lentils, peas	Maintenance of normal cell functions, formation of bones and teeth, as adenosine tri-phosphate (ATP), DNA and membrane synthesis, as well as protein phosphorylation
Potassium	C<9 - 3,800 mg C9-18 - 4,700 mg M<50 - 4,700 mg M>50 - 4,700 mg W<50 - 4,700 mg W>50 - 4,700 mg Wp - 4,700 mg Wl - 5,100 mg	Vegetable: spinach, cantaloupe, tomato, beet greens, breadfruit, avocado Fruit: banana, orange, Others: coconut, fufu, yam, potato, sweet potato Salmon	Electrolyte and cell homeostasis, regulates action potential in neurons
Sodium	C<9 - 1,200 mg C9-18 - 1,500 mg M<50 - 1,500 mg M>50 - 1,300 mg W<50 - 1,500 mg W>50 - 1,300 mg Wp - 1,500 mg Wl - 1,500 mg	Dietary salt Processed food: bread, rolls, pizza, sandwiches, cheese. Others: eggs and chicken, fruits, vegetables, legumes	Electrolyte and cell homeostasis, action potentials transmitting in neurons
Sulphur	Not available	Vegetable: garlic, onions, avocado, tomatoes, mustard Fruit: banana, pineapple, watermelon, Breast milk, meats, poultry, fish, eggs legumes and nuts Beverages: tea and cocoa	Constituent of amino acids, proteins, enzymes, vitamins and other biomolecules, essential for the building body's tissues and organs
Trace			
Boron	C<9 – 6 mg C9-18 – 17 mg M<50 – 20 mg M>50 – 20 mg W<50- 20 mg W>50- 20 mg Wp - 20 mg Wl - 20 mg	Fruit: peach, almond, grapes, apricots, apple, orange, banana Vegetable: broccoli, dates, onion, carrot Nut: hazelnuts, olive, brazil nuts, walnut, cashew nuts potato, lentils, chickpeas honey, peanut butter wine	Essential for metabolic activities in the body: anti-oxidation, bone maintenance, wound healing, regulation of hormone, vitamin and magnesium activities, improvement of brain electrical activity and cognitive performance
Chromium	C<9 - 15 µg C9-18 - 24 µg M<50 - 35 µg M>50 - 30 µg W<50 - 25 µg W>50 - 20 µg Wp - 30 µg Wl - 55 µg	Meats, grain products, fruits, vegetables, nuts, spices, brewer's yeast, beer, wine	Regulates glucose levels and essential in brain function
Cobalt	Not available	Vegetable: onions, potato, beetroot, cabbage, garlic, spinach, carrots Legumes and grains: oats, green peas, lentils, cereal, millet Fruit: strawberry, apple, pear, grapes, and apricot. Animal product: poultry, liver, heart, kidney. Dairy: milk, yogurt Sea food: squids, lobster, mackerel, oysters, crab, salmon	Red blood cells and myelin sheath syntheses, facilitates thyroid hormones production regulates RNA and DNA development, boosts immune system, aids iron absorption

Copper	C<9 - 440 µg C9-18 - 890 µg M<50 - 900 µg M>50 - 900 µg W<50 - 900 µg W>50 - 900 µg Wp - 1,000 µg Wl – 1,300 µg	Animal: beef, liver, turkey, Dairy: yogurt, milk Sea food: oysters, crab, salmon Vegetable: spinach, avocado, tomatoes Fruit: apple	Cofactor for several enzymes, energy production, iron metabolism, neuropeptide activation, connective tissue neurotransmitter syntheses, carbohydrate metabolism, potentiation of insulin action, reduced serum triglyceride
Fluoride	C<9 - 1 mg C9-18 - 3 mg M<50 - 4 mg M>50 - 4 mg W<50 - 3 mg W>50 - 3 mg Wp - 3 mg Wl - 3 mg	Tea, coffee Seafood: shrimp, tuna Fruit: grapefruit, apple, Vegetable: corn, avocado, asparagus, Animal: meat Dairy: yogurt, cheese, milk	Stimulates new bone formation, inhibits or reverses the initiation and progression of dental caries
Iodine	C<9 - 90 µg C9-18 - 150 µg M<50 - 150 µg M>50 - 150 µg W<50 - 150 µg W>50 - 150 µg Wp - 220 µg Wl - 290 µg	Seaweed, fish and other seafood Eggs, breast milk	Thyroid hormone synthesis and normal neurological development
Iron	C<9 - 10 mg C9-18 - 15 mg M<50 - 8 mg M>50 - 8 mg W<50 - 18 mg W>50 - 8 mg Wp - 27 mg Wl - 9 mg	Meat and seafood nuts, beans, vegetables, and fortified grain products. Cereal breast milk	Cofactor for numerous enzymatic reactions, critical for motor and cognitive development
Manganese	C<9 - 1.5 mg C9-18 - 1.6 mg M<50 - 2.3 mg M>50 - 2.3 mg W<50 - 1.8 mg W>50 - 1.8 mg Wp - 2 mg Wl - 2.6 mg	whole grains, oysters, mussels, nuts, soybeans and other legumes, rice, leafy vegetables, coffee, tea, black pepper, grain products, tea	cofactor for many enzymes involving amino acid, cholesterol, and carbohydrate metabolism; reactive oxygen species scavenging; bone formation; reproduction; immune response; and blood clotting and haemostasis
Molybdenum	C<9 - 22 µg C9-18 - 43 µg M<50 - 45 µg M>50 - 45 µg W<50 - 45 µg W>50 - 45 µg Wp - 50 µg Wl - 50 µg	Legumes, whole grains, nuts, and beef liver cereal grains, leafy vegetables, beef, liver, milk, cheese	Activates the antioxidant enzymes
Selenium	C<9 - 30 µg C9-18 - 55 µg M<50 - 55 µg M>50 - 55 µg W<50 - 55 µg W>50 - 55 µg Wp - 60 µg Wl - 70 µg	Seafoods, meats, liver, cereals and other grains, and dairy products, poultry, fish, eggs	Essential in some enzymatic actions and the maintenance of the antioxidant capacity of the brain, normal immune system and thyroid gland functioning
Zinc	C<9 - 5 mg C9-18 - 9 mg M<50 - 11 mg M>50 - 11 mg W<50 - 8 mg W>50 - 8 mg Wp - 11 mg Wl - 12 mg	Seafood: Oyster, crab, lobster Meat and poultry beans, nuts, whole grains, and dairy products wheat, baked beans, , Fruit: cashews, almonds.	Involved in molecular synthesis of DNA, RNA, and proteins, promotes immune functions and healthy pregnancy, decreases diarrhoea and respiratory infections

C<9-children < 9 years; C9-18 – children between 9-18 years; M<50 – men < 50 years; M>50 – men > 50 years; W<50 - women < 50 years; W>50 - women > 50 years; Wp – pregnant women; Wl – lactating women [31, 117, 118, 139-143]

A brief review of these functional roles is presented as follows:

Metabolic activities

Several metabolic activities in the body are regulated by the action of micronutrients [35]. These include the co-enzyme effects of vitamins B and K, which complement each other in their functions. These co-enzyme effects affect glucose and energy metabolism, the synthesis of amino acid, nucleotide, neurotransmitter and fatty acid [21, 22, 35]. Vitamins D and E are also involved in metabolic activities. Vitamin D regulates calcium homeostasis [71], while vitamin E regulates the activation of protein kinase C [72, 73]. Minerals, including boron, fluoride and selenium, also regulate several metabolic activities that are essential to hormonal, vitamin and magnesium activities [74].

Enzymatic activities

Several enzymatic activities in the body are regulated by micronutrients, which in turn influence their metabolism [23, 35]. While vitamin D is metabolized by the cytochrome P450 superfamily [24], vitamin K as well as boron, fluoride and selenium are essential for different enzymatic activities. Vitamin K acts as a cofactor of gamma-glutamyl carboxylase, while boron is essential for hormonal, vitamin and magnesium activities [25, 26, 74]. Iron acts as a cofactor for numerous enzymatic reactions but requires vitamins and other minerals, including copper and fluoride, for absorption into the body [74]. Magnesium, manganese and fluoride act as cofactors in many enzymatic reactions, particularly those involving amino acid, cholesterol and carbohydrate metabolism [17, 27].

Bone and growth development

Micronutrients, including vitamins A, C, D and K, as well as calcium, boron, fluorine, iodine, manganese and phosphorus, are necessary for the development, growth and maintenance of bones and teeth [17, 26, 27]. While vitamin C, calcium and iodine maintain bones and teeth, iodine also stimulates the formation of new bone and inhibits or reverses the development and progression of dental caries [17].

Neuronal and brain function

Water and fat-soluble vitamins and minerals are necessary for the development and function of neurons [21, 22]. Vitamins A, B, C, D and K as well as iodine are necessary for the regulation of neurodevelopment and function and for the formation and utilisation of glutamine, noradrenaline, dopamine and serotonin [3, 21, 22, 28]. While vitamins B9, B12 and C are essential for the synthesis of monoamines, boron and iron are crucial for motor and cognitive development, performance and protection [21, 22]. The B vitamins are involved in synthesis of catecholamines and gamma-amino glutamic acid (GABA), while vitamin D is involved in the formation and utilisation of glutamine [22, 73, 75-77]. Calcium, chloride, magnesium, potassium and sodium are necessary for neural and synaptic transmission [78]. Chromium is essential for brain function, while cobalt and fluoride are, respectively, important for the synthesis of myelin sheaths, the activation of neuropeptides, and the synthesis of neurotransmitter in connective tissue [29].

Immune system

The immune system serves to prevent and protect against the invasion of microorganism invasion and thus preserves health [30]. Vitamins A, B5 and C as well as copper, manganese, selenium and zinc are necessary for these immune functions, as they have both anti-inflammatory and pro-inflammatory effects [31, 32]. Manganese also regulates the polarisation of macrophages from pro-inflammation to anti-inflammation [33].

Energy production

Vitamins B and C as well as fluoride, iron and magnesium, are involved in energy production. While vitamin C is needed by the dioxygenase enzymes for the biosynthesis of carnitine, the B vitamins are involved as cofactors [34, 35]. The minerals regulate the oxygen content for energy production [34]. Phosphorus is an essential component of adenosine triphosphate (ATP) and is involved in protein phosphorylation [36]. Chromium regulates glucose and lipid homeostasis, which are essential for energy production [37].

Antioxidation

Vitamins C and E are natural antioxidants that inhibit the production of reactive oxygen species molecules and protect the cell membrane. Vitamin C scavenges reactive oxygen species, while vitamin E neutralises lipid hydroperoxyl radicals [38]. Molybdenum activates the antioxidant enzymes, while boron and selenium maintain the antioxidant capacity [29]. Manganese scavenges reactive oxygen species in the cells [39].

Cardiovascular system

Calcium is involved in regulation of the heartbeat and fluid balance [40, 41]. In the muscles, calcium binds to tropomyosin or calmodulin, which leads to the activation of myosin and actin and subsequently to muscle contraction [41, 42]. Calcium also mediates cell responses to hormones, including vasopressin [43].

Blood production and wound healing

Micronutrients are involved in the formation and maintenance of blood [44, 45]. Vitamins B12 and B9 are essential for hematopoiesis and, together with iron, play a crucial role in erythropoiesis [45]. During differentiation, vitamins B9 and B12 are required by the erythroblasts for proliferation. Iron, a component of haemoglobin, and cobalt are involved in the formation of red blood cells [44, 45]. Vitamin A helps in the development of erythroblasts from progenitor stem cells, while vitamin C promotes iron absorption [46, 47]. Vitamin C and boron also aid

in wound healing, which is important for the protective epithelial barrier and the restoration of tissue volume and strength [48, 49]. Vitamin E regulates platelet aggregation, while vitamin K, calcium and manganese accelerate tissue factor-induced coagulation, which is necessary for blood clotting [31, 50, 51].

Vision

Vitamins A, C and E and zinc, along with other nutrients, are important for the maintenance of the eyes and vision [52]. Vitamin A enables vision by producing rhodopsin, an essential protein that absorbs light in the rods in the eyes. Vitamins C and E act through their anti-oxidative mechanisms, eliminating reactive oxygen species and protecting the eye [53]. There is evidence of a role for vitamin K in vision, even though it is still in the speculative stage [54]. Zinc regulates vision by modulating autophagy in a diseased condition [55]. However, the effect of zinc is not yet fully understood.

Thyroid gland

The thyroid gland is an endocrine gland that synthesises tri-iodothyronine and tetra-iodothyronine hormones, which are necessary for the regulation of the body's metabolism [56]. The functions of this gland are moderated by the effects of vitamins A, B12, D and E, as well as cobalt, iodine, selenium, iron and zinc [57, 58]. How these micronutrients perform their roles is not fully understood.

Skeletal muscle action

Vitamin D is essential for the function of skeletal muscle, regeneration and health. It regulates the homeostasis of calcium ion, which in turn regulates the muscle contraction, as well as other functions [59]. Calcium is involved in muscle contraction by binding to myosin [41, 42].

Haemostasis

Vitamin K is essential for glomerular filtration, which is necessary for urine formation, where calcium regulates body fluid balance [40, 41]. Additionally, chloride, potassium and sodium are involved in homeostasis of electrolytes and cells [60], thus regulating fluid balance.

Other activities

Vitamins B1 and B2 have the effect of anti-nociception [61], thereby regulating pain sensation. Vitamin K is essential for sperm maturation, intestinal integrity, vascular elasticity, beta cell proliferation and insulin production, the suppression of gut risk microbe, the activation of vitamin K-dependent protein, adipogenesis and anti-inflammation [62, 63]. Vitamin C synthesises collagen, carnitine and cartilage [64]. Copper and phosphorus regulate the development of RNA and DNA [36, 65].

The short supplies of these micronutrients in food require supplements with adequate contents for maximum health benefits. Additionally, a poor diet, illness, adverse effects of certain medications, an unhealthy lifestyle or debilitating conditions due to natural processes of life, such as menstruation and old age also justify the need for dietary supplements.

Micronutrient supplements for communicable and non-communicable diseases

The continuing need for micronutrient supplements may not decline in the face of worldwide food crises, particularly those resulting from global warming and insecurity [5, 6]. Growing economic problems, especially in developing countries, have also warranted the intake of micronutrient-rich foods and herbs to treat essential diseases [3, 7, 8, 12]. Even when the Recommended Daily Allowances (RDA) are sufficient, micronutrient supplementation is still required in healthy adults [6, 35]. The reason for this is that the active and demanding lifestyle of adults often leads to fatigue and lack of energy. Therefore, micronutrient supplementation is needed to protect against impaired cellular energy production [35]. These supplements can also strengthen the immune system against unpredictable disease [31, 79, 80]. In prenatal and postnatal life, micronutrients are essential for protection against pregnancy- and infant-related mortality and reduced infant gut microbiota [12, 81, 82]. The protective effect of these micronutrients has been reported under experimental conditions [8, 66, 81]. They alleviate the impairment of motor function in experimental Parkinsonism [83], mitigate experimentally induced neurological changes and protect against experimentally induced brain dysfunction [75, 84, 85]. But can these supplements prevent or protect against diseases? There are several reports about the possibilities, but some of them are also controversial in the sense that large studies do not show the benefits [86]. Recent reviews have suggested the targeted application of micronutrients in combating communicable and non-communicable diseases [17, 19, 20].

In clinical practices, micronutrients can act against communicable diseases either by directly interfering with and modifying the defense mechanisms of the target organism or by activating the immune system of host [87, 88] and thus strengthening the immune system [12, 23, 24, 26]. These mechanisms of action are very important, especially for diseases with insufficient knowledge of treatments [31]. Micronutrients are reported to reduce viral loads in certain disease conditions [17, 19, 20, 88, 89]. Their supplementations reduced the progression of HIV disease and the incidence of HIV-associated complications in infected women [89] as well as mortality in patients with Ebola virus disease [90]. The success with other viral infections has led to the proposal to use them in the treatment of COVID-19 patients [87, 91]. These micronutrient supplements also reduced the incidence of clinical malaria [92, 93], improved anti-malarial parameters and survival

[94] and improved recovery in influenza [95].

In the comorbidity of viral diseases such as HIV and malaria, these micronutrients help to reduce the development of symptomatic malaria in HIV-infected women [96] as well as the incidence and prevalence of pneumonia in children with HIV-1 infection [97].

Micro- and macronutrients have been reported to have great potential in the treatment of non-communicable diseases (NCDs) [72, 98, 99]. These micronutrients can support the function of macronutrients or the efficacy of agents needed for such NCD treatments [98, 99]. It is reported that micronutrients help prevent chronic obstructive pulmonary disease and lung cancer [98] and reduce the severity of respiratory impairment in elderly men with chronic obstructive pulmonary disease [99].

Therefore, micronutrients can be used in the treatment of cardiovascular disease, and their supplementation also improves patients with cardiovascular disease and cancers [8, 72, 73, 100-102]. Micronutrient supplementation can also reduce the risk of pre-eclampsia and high blood pressure in pregnant women [103, 104] and improve arterial blood pressure in diabetic and non-diabetic patients [105-108].

Supplementation with multiple micronutrients ameliorates chronic gastrointestinal tract (GIT) diseases [100] and oral precancerous conditions, such as submucous fibrosis [109]. These results have led to its use being recommended against toxic free radicals generated during immunotherapy and tumour metabolism [110]. Taking vitamin D supplementation in patients with hypothyroidism improved serum thyroid stimulating hormone and calcium concentrations [111].

Supplementation with these micronutrients has been reported to provide benefits in certain genetic diseases, such as βeta (β)-thalassemia [112-114]. In particular, β-thalassemia is caused by defects in the β-globin genes that lead to decreased haemoglobin production [112]. Therefore, vitamin E supplementation prevents damage to the erythrocyte membrane and counteracts lipid peroxidation processes, which helps to alleviate the symptoms of the disease [112-114].

In the area of mental health, micronutrients improve motor and cognitive function in elderly patients with cognitive-related diseases [76], alleviate oxidative damage and reduce stress and anxiety in diabetic patients [31, 67, 115]. This thus contributes to the recovery from traumatic brain injury [71] and reverses depressive symptoms [8, 73, 77, 101, 116-120].

Most of the biological functions in disease prevention are listed in Table 1 and Table 2. In contrast, negative or no benefits have also been reported for micronutrient supplements [81, 118]. For example, micronutrient supplementation did not protect against the incidence or severity of respiratory infections in low-birth-weight neonates nor did it have an impact on maternal mortality [81, 118], or simultaneously promote colonisation of a specific infant gut microbiota [82]. Other findings have shown no consistency in reducing the risk of stroke and little or no effect on the risk of preterm birth [121, 122].

The corona virus disease: can micronutrients help?

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has impacted the world with over 769 million confirmed cases and over 6.9 million deaths [123]. This disease is reported to modify the host immune system, leading to long-term inflammation and resulting tissue damage [124]. Several reviews have indicated the important roles of micronutrients in immune response [18, 20, 32, 80, 87, 125], with these roles also applying to the treatment of COVID-19 [20, 87, 126, 127]. Deficiencies of these micronutrients have been reported in increased infection and severity of COVID-19 [128-132].

Vitamins C and D, zinc and selenium, which are essential micronutrients, have been reported to improve the treatment of COVID-19 and reduce mortality [128, 133]. The effect of these micronutrients against COVID-19 is generally to strengthen the immune system by being available for every metabolic process. The specific role of micronutrients against COVID-19 is still elusive. Nevertheless, a suggested mechanism of action against COVID-19 is the activation of platelets in patients [134].

Micronutrients and disease management: the future is still bright

The present and future need for micronutrients for health cannot be written off even though their role in diseases is inconsistent. For instance, most diseases are due to micronutrient deficiencies, and their supplementation tends to alleviate the symptoms, if not the entire disease [15, 83, 90, 92, 95, 96, 135, 136]. In another instance, the efficacy of mono and combined therapies with various drugs against diseases may not be successful if there are no adjuvants in micronutrients because their associated toxicities often stem from such treatments [137]. Although drug-drug interactions may occur sometimes [137, 138], micronutrients need not be written off in the treatment of disease now or in the future.

Conclusion

The importance of micronutrients in the diet or in the form of food supplements cannot be overemphasised, as they are responsible for numerous enzymatic, metabolic and developmental processes, and also play an important role in the recovery of some diseases. Taking supplements usually compensates for deficiencies caused by inadequate diet, illness or social behaviours that often lead to deficiencies.

There are reports on the preventive and protective role of micronutrient supplements in health and disease. However, due to inconsistent data and limited information on the role of micronutrients in disease, it is difficult to recommend them exclusively for the treatment and prevention of such diseases, but their application is still beneficial.

Authors' contribution

Moses B. Ekong: conceptualization, supervision, critical revision, and final approval. Agnes A. Nwakanma: Collected data; supervised; drafted manuscript. Clementina F. Iniodu: Collected data; drafted manuscript.

Conflict of interests

The authors declare no conflict of interest.

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