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# New Advances about the Effect of Vitamins on Human Health: Vitamins Supplements and Nutritional Aspects

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Additional information is available at the end of the chapter

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## Abstract

The early twentieth century was a crucial period for the identification and biological-chemical-physical characterisation of vitamins. From then until now, many studies have attempted to clarify into detail the biological role of the vitamins in humans and their direct connection with certain diseases, either in a negative way (appearance of deficiency diseases due to vitamin deficiency) or a positive way (use of vitamins to treat diseases and/or to improve human health). The aim of this work is to analyse, from an integrative point of view, the information about vitamins and their effects on human health, and to identify direct correlations between these compounds and health. The effects of vitamins supplements on diet are also explored. The analysis of the results shows that it is impossible to establish robust and universal conclusions about the benefit of vitamin supplementation on human health beyond the prevention and/or treatment of deficiency states.

**Keywords:** nutrition, vitamins, human health, antioxidants, dietary supplements, multivitamins

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## 1. Introduction

Human nutrition, as a field of knowledge, had a great impact at the beginning of the twentieth century. From 1912, experiments such as those developed by English biochemist Frederick Hopkins (1861–1947) demonstrated the existence of certain organic substances in food that are essential for health. Hopkins called them ‘accessory food factors’ [1–3]. Shortly after that discoveries, the Polish biochemist Casimir Funk (1884–1967) proposed the term ‘vitamins’ to

identify the substances previously termed 'accessory food factors' [2, 3]. The etymology of the term vitamin derives from the Latin 'vita' (life) and 'amina'; Funk concluded that these substances were necessary for life and most of them contained an amino group [1, 4]. Thus, in the early sixties, the identification of essential nutrients necessary to support human life and health (macronutrients, micronutrients and trace elements) was almost concluded [4].

In the last half of last century, all vitamins were identified, their chemical structures were determined and natural sources from which vitamins can be obtained were described in detail. The biological role of each vitamin, their connections with several metabolic pathways and human pathologies and their importance in human nutritional processes were also quickly established [2, 4]. Besides, advances in chemical analysis/technologies during the last three decades have provided the tools to produce vitamins *in vitro* (even at large scale). Consequently, vitamins can be currently obtained by chemical synthesis, by isolation of natural sources (fat-soluble vitamins) or by microbial biotechnology (mainly water-soluble vitamins).

Thus, several human pathologies based on vitamins deficiency can be fully eradicated or their prevalence decreases substantially thanks to (i) promotion of good nutrition practices and (ii) use of dietary supplements containing mainly vitamins and trace elements. Even so, malnutrition is still a massive problem, particularly in some geographic regions characterised by poverty, poor nutrition understanding and practices and deficient sanitation and food security.

During the last five decades, several scientific-technical reports have confirmed and/or suggested new biological roles and properties for vitamins in human beings. Despite a large amount of existing information, there are very few integrative studies carried out on the effect of the vitamins on human health. In this sense, the work here presented summarises the main recent evidences that provide an integrated and updated analysis about the effect of vitamins in human health. The main aim is to understand how the use of vitamins (from food or from dietary supplements containing vitamins) can improve human health or the evolution of some specific disease.

## 2. General aspects of vitamins

### 2.1. Definition and classification

Vitamins are organic micronutrients mainly synthesised by plants and microorganisms, which do not provide energy. Animals are not able to synthesise them, consequently, these essential micronutrients must be supplied by the diet in small amounts or even trace amounts (micrograms or milligrammes per day) for the maintenance of the metabolic functions of most animal cells [5, 6]. However, some vitamins can be synthesised in varying concentrations by humans. Thus, vitamin D and niacin are endogenously synthesised (in the skin by exposure to the sun or from the amino acid tryptophan, respectively) [7, 8]. On the other hand, vitamins such as K2, B1, B2 and biotin are synthesised by intestinal bacteria [9]. Generally, this

endogenous synthesis is not enough to cover daily needs, so dietary intake is required [8, 10]. Most of the vitamins were identified related to the diagnosis of the diseases associated with their deficiency [2, 11]. Thus, these diseases are termed 'deficiency diseases'.

Two groups of vitamins are distinguished based on their solubility (fat-soluble and water-soluble vitamins) [6] (**Table 1**). Each of these two groups exhibit significantly different physical-chemical-biological characteristics. The alphabetic nomenclature indicates the chronology of its discovery; however, the subsequent observation that vitamin B consisted of multiple compounds, gave rise to numerical nomenclature. The gaps in numbering are due to the removal of several substances that were initially described as vitamins [8, 10].

Besides, vitamins are also classified by their biological role, which constitutes a more scientific approach to the current reality (Section 2.3 display details about the biological roles).

## 2.2. Physical-chemical properties

Each vitamin is a family of chemically related compounds that share qualitatively biological activities and may vary in aspects related to their bioactivity and bio assimilation. Therefore, the common name of the vitamin (i.e. vitamin A) is, in fact, a generic descriptor for all active analogues or relevant vitamin derivatives [12]. **Table 2** summarises the main physical-chemical properties.

## 2.3. Biological roles

Vitamins play an important role in several metabolic pathways, acting closely associated with many of the enzymes that catalyse the reactions involved in these metabolic processes [10, 13, 14].

Fat-soluble vitamins	Water-soluble vitamins
Vitamin A or Retinol	Vitamin B1 or Thiamine
Vitamin D or Calciferol	Vitamin B2 or Riboflavin
Vitamin E or $\alpha$ -Tocopherol	Vitamin B3 or Niacin
Vitamin K or Phylloquinone	Vitamin B5 or Pantothenic acid
	Vitamin B6 or Pyridoxine
	Vitamin B7 or Biotin
	Vitamin B9 or Folic acid
	Vitamin B12 or Cobalamin
	Vitamin C or Ascorbic acid
Soluble in fats	Soluble in water
They do not contain nitrogen	They contain nitrogen (except vitamin C)
Require bile salts and fats for absorption	Easily absorbed
Normally not excreted in the urine	They present urinary excretion threshold (Unlikely toxicity)
No daily or usual intake is required	Almost daily intake is required
Hypervitaminosis can cause toxicity	Not stored in the body (Exception: vitamin B12 in liver)
Liver and adipose tissue storage	

Note. Underlined: Name mainly used in the scientific literature.

**Table 1.** Classification and differences of vitamins based on their solubility [6].

Vitamin	Derivatives	Chemical formula	MW	Maximum absorption (nm)	Melting point (°C)	Colour/State
<b>A (retinol)</b>	Retinol	$C_{20}H_{30}O$	286.4	319–328	62–64	Yellow/crystal
	Retinal	$C_{20}H_{28}O$	284.4	373	61–64	Orange/crystal
	Retinoic acid	$C_{20}H_{28}O_2$	300.4	350–354	180–182	Yellow/crystal
<b>D (cholecalciferol)</b>	Cholecalciferol (vitaminD3)	$C_{27}H_{44}O$	384.6	265	84–85	White/crystal
	Ergocalciferol (vitaminD2)	$C_{28}H_{44}O$	396.7	264	115–118	
<b>E (<math>\alpha</math>-tocopherol)</b>	$\alpha$ -tocopherol	$C_{29}H_{50}O_2$	430.7	292	2.5	Yellow/oil
	$\gamma$ -tocopherol	$C_{28}H_{48}O_2$	416.7	298	–2.4	
<b>K (phyloquinone)</b>	Phylloquinone(K1Menaquinone-s (K2 <sub>n</sub> ))	$C_{31}H_{46}O_2$	450.7	242	-	Yellow/oil
		-	444.7–649.2	243–270	35–54	Yellow/crystal
	Menadione(K3)	$C_{11}H_8O_2$	172.2	-	105–107	Yellow/crystal
<b>B1(thiamine)</b>	Thiamine	$C_{12}H_{17}N_4OS^+$	337.3	-	246–250	White/Crystals
<b>B2 (riboflavin)</b>	Riboflavin	$C_{17}H_{20}N_4O_6$	376.4	260	278	Orange-Yellow/ Crystal
<b>B3 (niacin)</b>	Nicotinic acid	$C_6H_5NO_2$	123.1	260	237	White/Crystal
	Nicotinamide	$C_6H_6NO_2$	122.1	261	128–131	
<b>B5 (pantothenic acid)</b>	Pantothenic acid	$C_9H_{17}NO_5$	219.2	204	-	Clear/oil
<b>B6 (pyridoxine)</b>	Pyridoxol	$C_8H_{11}NO_3$	205.6	253	206–208	White/Crystal
	Pyridoxal	$C_8H_9NO_3$	203.6	390	165	
	Pyridoxamine	$C_8H_{12}N_2O_2$	241.1	253	226	
<b>B7 (biotin)</b>	Biotin	$C_{10}H_{16}N_2O_3S$	244.3	204	232	Colourless/Crystal
<b>B9 (folic acid)</b>	Folic acid	$C_{19}H_{19}N_7O_6$	441.1	282	-	-
<b>B12 (cobalamin)</b>	Cyanocobalamin	$C_{63}H_{88}CoN_{14}O_{14}P$	1355.4	278	-	Dark red/Crystal
<b>C (ascorbic acid)</b>	Ascorbic acid	$C_6H_8O_6$	176.1	245	190–192	White/Crystals

**Table 2.** Physic-chemical properties of vitamins and the most relevant derivatives (Adapted from Combs, [12]; <https://www.ncbi.nlm.nih.gov/pccompound>; <http://www.lipidbank.jp/>).

Using the 'biological role' as criteria, vitamins are classified into five groups:

- Vitamins acting as coenzymes: B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine) and B7 (biotin).
- Antioxidant vitamins: E ( $\alpha$ -tocopherol) and C (ascorbic acid).
- Vitamins showing hormonal functions: A (retinol) and D (calciferol)
- Vitamins that act in the cellular proliferation: B9 (Folic acid), B12 (cobalamin).
- The vitamins involved in coagulation: K or phyloquinone.

Thus, vitamins belonging to the group B work together at the cellular level and they are essential for neurological functioning and central metabolism [15]. A deficient intake of one or more than one of them may hinder the use of the other vitamins of group B. On the other hand, antioxidant vitamins protect against cell damage caused by the oxidative attack of free radicals reactive nitrogen species (ROS), Reactive nitrogen species (RNS), avoiding the destruction of the body's tissues. This group of vitamins prevent the development of a large number of degenerative diseases, associated with ageing and oxidative stress, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, cancer and myocardial infarction (heart attack), among others [16, 17]. In addition, some vitamins assume additional endocrine functions [18]. Consequently, the deficiency of a vitamin causes metabolic processes imbalances. This fact results in clinical signs or diseases of different health impact based on the level of deficiency. **Table 3** summarises the main biological roles played by vitamins and anomalies in human health due to vitamin excess (toxic effects in the case of liposoluble vitamins) or vitamin deficiency.

Vitamin	Biological roles	Clinical signs of deficiency	Toxic effects
Vitamin A (retinol)	Cellular repair and maintenance. Immune response. Development of NS. Normal vision. Foetal development. Reproduction. Bone growth. Antioxidant activity.	Xerophthalmia, night blindness, keratinization of the corneal epithelium, dry mucous membranes	Anorexia, weight loss, extreme irritability, diplopia, alopecia, headache, bone abnormalities, liver damages, birth defects
Vitamin D (cholecalciferol)	Bone and dental mineralisation. Absorption and metabolism of calcium and phosphorus.	Rickets (in children), osteomalacia (in adults) and osteoporosis	Hypercalciuria and hypercalcemia with soft tissue calcifications, renal and cardiovascular damage
Vitamin E ( $\alpha$ -tocopherol)	Powerful antioxidant. Synthesis of heme group. Antitoxic function.	Peripheral neuropathy, spinocerebellar ataxia and pigmentary retinopathy.	Haemorrhagic toxicity, headache, fatigue, nausea, double vision, muscular pains, creatinurea, gastrointestinal distress
Vitamin K (phyloquinone)	Blood clotting. Protein synthesis. Bone metabolism	Haemorrhages.	Menadione (synthetic form) causes liver damage, jaundice and haemolytic anaemia in newborns

Vitamin	Biological roles	Clinical signs of deficiency	Toxic effects
VitaminB1 (thiamine)	Macronutrient metabolism. Neuronal function.	Beriberi <sup>1</sup> . Wernicke-Korsakoff syndrome. Polyneuritis. Heart failure. Anorexia and gastric atony	Not observed
VitaminB2 (riboflavin)	Energy metabolism. Ocular function. Antibody and red blood cells formation. Mucosal maintenance.	Oral-ocular-genital syndrome <sup>2</sup> .	Not observed
VitaminB3 (niacin)	Macronutrient metabolism. Sex hormone production. Glycogen synthesis.	Pellagra <sup>3</sup> (dermatitis, dementia and diarrhoea).	Hepatotoxicity, flushing <sup>4</sup> , nausea, blurred vision and IGT
VitaminB5 (pantothenic acid)	Energy metabolism. Antibody synthesis. Corticosteroid synthesis Cholesterol synthesis	Hypertension, gastrointestinal disturbances, muscular cramps, hypersensitivity, neurological disorders	Not observed
VitaminB6 (pyridoxine)	Fat and protein metabolism DNA and RNA synthesis Haemoglobin synthesis. Antibody production. Electrolyte balance. Neuronal function. Conversion of tryptophan to niacin	Neuropathy (paraesthesia). Epileptiform convulsions in infants. Hypochromic anaemia, seborrheic dermatitis and glossitis	Sensory neuropathy and skin disorders.
VitaminB7 (biotin)	Energy metabolism. Cell growth Fatty acids amino acids and glycogen synthesis	Dermatitis, conjunctivitis, alopecia and abnormalities of the CNS (depression, hallucinations and paraesthesia)	Not observed
Vitamin B9 (folic acid)	DNA and RNA synthesis Growth and cell division Leukocytes and erythrocytes formation and maturation. Folic acid metabolism	Macrocytic anaemia	Neurological complications in people with vitamin B12 deficiency
VitaminB12 (cobalamin)	Lipid and protein metabolism Red blood cells maturation. Iron absorption. DNA and RNA synthesis. Neuronal function	Hematologic (macrocytic anaemia), paraesthesia	Not observed
Vitamin C (ascorbic acid)	Multiple functions as coenzyme Iron absorption. Wound healing Antioxidant. Corticosteroid synthesis	Scurvy <sup>5</sup> . Sjögren syndrome, gum inflammation, dyspnoea, oedema y fatigue. Bone abnormalities, haemorrhagic symptoms and anaemia	Diarrhoea and other gastrointestinal disturbances

NS: Nervous system; CNS: central nervous system; IGT: impaired glucose tolerance.

<sup>1</sup>First nutritional deficiency described, typical of populations subsisting on diets in which polished ('white') rice is the major food. The pathology leads to weight loss, heart disorders and neurological dysfunction.

<sup>2</sup>Affectation of the mucous membranes, tongue (glossitis), lips (cheilitis) and hypervascularization of the cornea.

<sup>3</sup>In populations subsisting on diets in which maize is the major food.

<sup>4</sup>Head and neck redness.

<sup>5</sup>Signs and symptoms include: follicular hyperkeratosis, petechial, ecchymosis, coiled broken hairs, swollen and bleeding gums, perifollicular bleeding, joint spasm, arthralgia and altered wound healing (IOM, [18]; Combs, [10]).

**Table 3.** Main biological functions, clinical signs of deficiency and toxic effects (caused by excessive intake, hypervitaminosis) of vitamins [8, 10, 14, 18–20].

### 3. Recommended dietary intakes

Most foods (exceptions: sucrose, refined grains and alcoholic beverages), provide vitamins in number and variable quantity [6]. However, there is not a single food containing all of them. Therefore, the diets must be mixed and balanced thus supplying the vitamins at the levels required by the body. When a food (or a diet) provides some or all the macronutrients but does not contain the necessary vitamins, it hinders the correct metabolism. Consequently, several official institutions around the world provide guides to recommend the optimum values of daily vitamins intake to promote health and to eradicate deficiency diseases.

The reference values of vitamin intake, allow preventing deficiency states and hypervitaminosis. **Table 4** shows the recommended dietary allowance (RDA) related to vitamins, which are focused on metabolic needs in the general population, and the maximum tolerable daily intake (UL) without risk of adverse health effects for the general population. These may vary between countries.

Vitamin	RDA	UL	Food sources
Vitamin A <sup>1</sup> (retinol)	2900 IU/d* (800 µg/d)	10,000 IU/d (3000 µg/d)	Liver, fish, dairy products, meat, egg yolk, butter, darkly coloured fruits and leafy vegetables
Vitamin D <sup>2</sup> (cholecalciferol)	600 IU/d* (15 µg/d)	2000 IU/d (50 µg)	Fish liver oils, fatty fish, egg yolk, fortified dairy products and fortified cereals
Vitamin E (α-tocopherol)	15 mg/d	1000 mg/d	Vegetable oils, unprocessed cereal grains, nuts, fruits, vegetables, meats
Vitamin K (phylloquinone)	90–120 µg/d	-	Green vegetables, Brussel sprouts, cabbage, plant oils and margarine
Vitamin B1 (thiamine)	1.2 mg/d	-	Enriched, fortified or whole-grain products, bread and bread products, mixed foods whose main ingredient is grain, cereals, potatoes, liver, pork and eggs
Vitamin B2 (riboflavin)	1.2 mg/d	-	Organ meats, milk, bread products and fortified cereals
Vitamin B3 (niacin)	15 mg/d	35 mg/d	Meat, fish, poultry, enriched and whole grain breads and bread products, fortified cereals and mushrooms
Vitamin B5 (pantothenic acid)	5 mg/d	-	Chicken, beef, potatoes, oats, cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli and whole grains
Vitamin B6 (pyridoxine)	1.3 mg/d	100 mg/d	Fortified cereals, organ meats, fortified soy-based meat substitutes and bananas
Vitamin B7 (biotin)	30 µg/d	-	Liver, egg yolk, pork and vegetables

Vitamin	RDA	UL	Food sources
Vitamin B9 (folic acid)	400 µg/d	1000 µg/d (1 mg/d)	Enriched cereal grains, dark leafy vegetables, enriched and whole grain breads, fortified cereals, liver and nuts
Vitamin B12 (cobalamin)	2.4 µg/d	-	Fortified cereals, meat, fish and poultry
Vitamin C (ascorbic acid)	80 mg/d	2000 mg/d	Citrus fruits, tomatoes, potatoes, Brussel sprouts, cauliflower, broccoli, strawberries, cabbage and spinach

\*RDAs for vitamins A and D are listed in both International Units (IUs) and micrograms (mg/day) or micrograms (µg/day). The hyphen (-) indicates that the UL is not determined due to lack of data on the adverse effects associated with the excessive intake of these vitamins.

<sup>1</sup> The vitamin A activity in foods is thus currently expressed as retinol equivalents (RE): 1 RE is defined as 1 µg of all-trans retinol, 6 µg of all-trans β-carotene, or 12 µg of another provitamin A carotenoids. Or it is expressed in IU (international units): 1 IU of vitamin A activity has been defined as equal either to 0.30 µg of all-trans retinol or to 0.60 µg of all-trans β-carotene.

<sup>2</sup> In the case of vitamin D, 1 µg calciferol = 40 IU of vitamin D, a value based on a minimum of sun exposure.

**Table 4.** Recommended dietary allowances (RDAs), tolerable upper intake level (UL) for healthy adults and main food sources containing the vitamins described [18], [https://fnic.nal.usda.gov/sites/fnic.nal.usda.gov/files/uploads/DRI\\_Vitamins.pdf](https://fnic.nal.usda.gov/sites/fnic.nal.usda.gov/files/uploads/DRI_Vitamins.pdf)].

Some vitamins can be supplied as provitamins, substances without vitamin activity that when metabolised, give rise to the formation of the corresponding vitamin [8, 12]. In some cases, it is possible to synthesise the vitamin from dietary compounds that apparently have no relation to it. For instance, nicotinic acid (vitamin B3) can be caused by the metabolic transformation of the amino acid tryptophan [8] or retinol (vitamin A), which can be obtained from beta-carotene (a pigment produced by some vegetables and microorganisms) [21].

#### 4. Bibliographic and bibliometric analysis of the selected information.

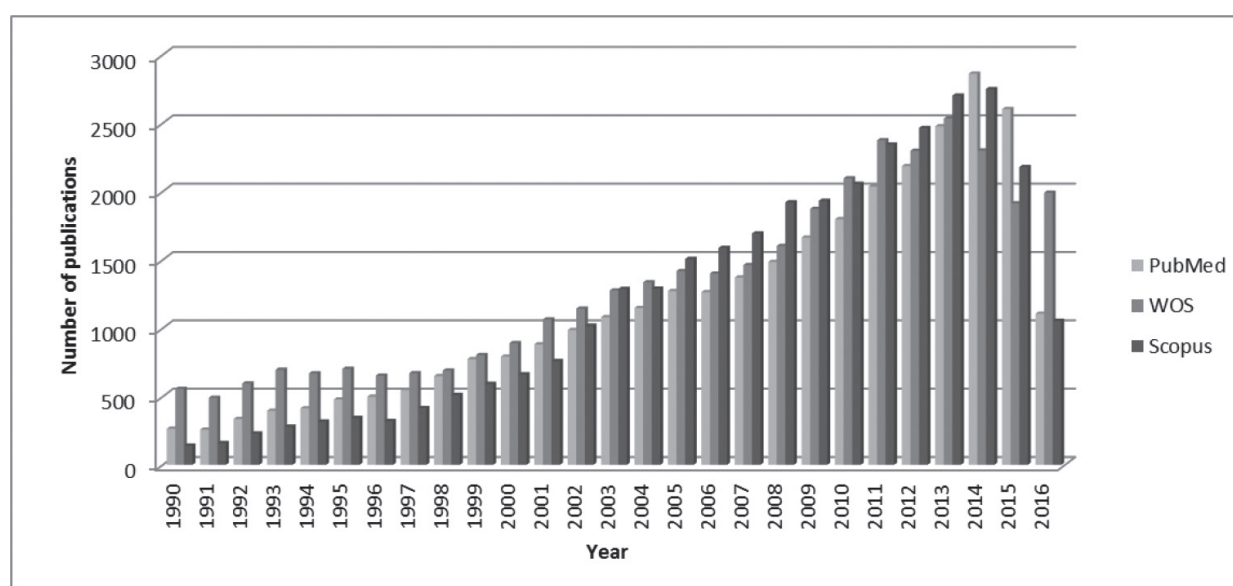
To identify the main recent scientific-technical works about vitamins and their effect in human beings, a bibliographic/bibliometric review has been made following PRISMA guide [22]. The classical scheme proposed by Vilanova [23] has been used to analyse and to assess the quality of the information obtained. The main aim of this analysis is to understand how the use of vitamins (from food or from dietary supplements containing vitamins) can improve human health or the evolution of some specific diseases.

To do the information search (manuscripts published during the last 27 years in English and Spanish), general and more specific databases were selected (<https://scholar.google.es/>; PubMed, <http://www.ncbi.nlm.nih.gov/pubmed>; Scopus, <https://www.scopus.com/>; Web of Science (WOS), <https://apps.webofknowledge.com/>). The keywords used to do the search were: all the names of the vitamins, 'vitamins & human health', 'vitamins & biological roles' and 'deficiency diseases'. These terms were previously identified through the

database 'MeSH' (medical subject heading) as suitable descriptors for the realisation of this work. Combinations of these keywords with the terms 'diet' and 'nutrition' were also used to identify as many sources as possible. All the following options were selected in the databases previously mentioned: 'Title/Abstract', 'article', 'clinical trial' and 'review'. Search finished in December 2016, the 15th. The research questions used to do the search and to select the information were: What is new about the knowledge of the effect of vitamins on human health? Is human health improving when multivitamin complexes are used?

**Figure 1** displays the results of the search just using the combination 'vitamins & human health'. Thanks to this keywords combination, 99,990 publications were identified (32,363 Pubmed; 35,127 WOS; 32,500 Scopus). About 60–77% of these publications are research articles (most of them clinical trials), 13–24% reviews and 5–11% are proceedings. Most of the items consulted (85%) belong to the field of medicine, followed by the fields of biochemistry, genetics and molecular biology (15%). To carry out this work, all the items were analysed by the three authors paying special attention to reviews and clinical trials. As it can be concluded from this figure, the last decade was particularly productive in terms of a number of publications analysing the effect of vitamins in human health or the use of vitamins as part of a treatment against certain pathologies.

To address the detailed analysis of the direct effects of vitamins in human health, described by each item identified (**Figure 1**), four categories or manuscripts were established: 1: experimental studies, clinical trials; 2: analytical observational studies (cohort studies; case-control studies); 3: Descriptive observational studies (series of cases; studies of incidence and prevalence); 4: Reviews, systematic reviews and/or meta-analysis. The main conclusions from this analysis are summarised in the following section.



**Figure 1.** Identification of publications of interest. Number of items reported in the last 27 years. Keywords: Vitamins & Human health.

## 5. New advances of the effect of the use of vitamins through the diet in human health as well as the treatment of several human diseases

From the database containing the publications of interest previously mentioned, 75% of them were analysed into detail to highlight what is new about the use of vitamins through the diet in human health as well as their use as part of the treatment of several human diseases. Most the publications analysed in this work suggest a possible effect of a vitamin (its derivatives, analogues or precursors), or combinations of vitamins in human health. However, the results presented in the majority these publications are not conclusive. Thus, most of them assume that it is not possible to attribute with certainty the effect observed due to inconsistencies in the design or implementation of the studies. In this sense, there are many aspects to discuss, which are following summarised:

- a) The standard method of medical science to establish and to compare the effectiveness of a substance in human beings is the clinical trial [24]. However, despite having strict inclusion criteria, these studies present some features that can affect the results. Some of the main features that may influence the results are: genetic background and style of life of the patient; non-specific effects and bioavailability of the vitamin/molecule tested; selection of the mechanism of action of the molecule tested; validity of the biomarkers used to determine the effect of a compound; the sample size (population) and the duration of the study (especially critical when the pathological condition under study takes decades to develop). All these aspects should be taken into account when interpreting the clinical results; otherwise, the associations observed are inadequately estimated of causality, and consequently, a direct relationship between the administration of a vitamin and effect on human health cannot be properly established.
- b) Observational studies are easier to perform in terms of methodology, but they lack the capacity to establish causality of phenomena.
- c) The meta-analysis presents a high level of scientific evidence, especially the meta-analysis of randomised controlled trials [24]. Meta-analysis is characterised by the high size of the study population, and therefore, they show better clinical significance. However, as a disadvantage, they usually are not feasible due to the difficulties of finding trials with the homogeneous design.

Therefore, despite a large number of publications on the vitamins and the potential uses of multi/vitamin supplements, there is no scientific evidence of beneficial effects in human health, beyond the prevention and/or treatment of deficiency states.

In this sense, the supplementation of food, as well as strategies to improve nutritional practices, have contributed to the eradication of deficiency diseases [25–28]. The main biological functions, clinical signs of deficiency and toxic effects of vitamins described until the end of the last century were previously discussed in Section 2.3 (**Table 3**). Recently, new correlations between vitamins and human health have been proposed. Details about the best described correlations between the use of vitamins on human health are following summarised:

**Vitamin A:** Diet supplementation has a positive effect on the blindness and the morbid-mortality in preschool-age children living in developing countries (<http://data.unicef.org/nutrition/vitamin-a.html>). Since 1960, clinical trials have shown that the disorders caused by vitamin A deficiency in developing countries can be prevented with regular dose and this supplementation significantly reduces infant mortality [29–31]. In relation to the other observed associations between vitamin A and certain diseases (**Table 5**), the evidence obtained do not allow definitive conclusions on the potential benefits of supplementation.

**Vitamin D:** The role of vitamin D in bone health is probably one of the better-supported relationships (**Tables 3 and 5**). The ‘new’ properties related to vitamin D are closely linked to the biological function already described. Thus, several meta-analyses of randomised controlled clinical studies conclude that vitamin D supplementation reduces the risk of falls (derived from the bone fragility) in a 19%, the risk of hip fracture in an 18% and the risk of non-vertebral

Name of the vitamin	Diseases or health states	Name of the vitamin	Diseases or health states
<b>Vitamin A (retinol)</b>	Eye diseases Mortality Cancer Anaemia	<b>Vitamin K (phylloquinone)</b>	Bone health CVD Cancer Mortality
<b>Vitamin E (α-tocopherol)</b>	CVD, cancer, mortality Alzheimer disease, immunity	<b>Vitamin D (cholecalciferol)</b>	Bone health, cancer, CVD Hypertension Autoimmune diseases Pregnancy Quality life Pulmonary infections Mortality
<b>Vitamin B1 (thiamine)</b>	Microalbuminuria in DM Cardiac function	<b>Vitamin B2 (riboflavin)</b>	Homocysteine levels in plasma Cancer Migraine
<b>Vitamin B3 (niacin)</b>	Atherosclerosis, Dyslipidaemias, Mortality, Diabetes, Cancer	<b>Vitamin B5 (pantothenic acid)</b>	Healing Acne Rheumatoid arthritis
<b>Vitamin B6 (pyridoxine)</b>	TD, Cancer, PMS, CTS Side effects of OCPs, CVA	<b>Vitamin B7 (biotin)</b>	DM Multiple sclerosis
<b>Vitamin B9 (folic acid)</b>	Birth defects, Vascular disease Renal disease, Cognitive Function, Cancer, DM, Childhood asthma, Childhood leukaemia	<b>Vitamin B12 (cobalamin)</b>	Cognitive function Congenital diseases
		<b>Vitamin C (ascorbic acid)</b>	Cancer, CVD, Pulmonary function, Cold, Stress, AMD

AMD: Age-related macular degeneration; CTS: Carpal tunnel syndrome; CVA: stroke (cerebrovascular accident); CVD: cardiovascular disease; DM: diabetes mellitus; OCPs: oral contraceptives; PMS: premenstrual syndrome; TD: tardive dyskinesia.

**Table 5.** New associations found between vitamins (deficiency or toxicity) and diseases or health states.

fractures in a 20% in older adults. The effect on the prevention of falls or fractures is reached using high doses of at least 700–1000 IU/day or at least 400 IU/day, respectively [32–35]. In addition, supplementation has been shown to have a beneficial effect on the balance and muscle strength [36]. The evidence-based clinical trials suggest that supplementation with vitamin D (1000 IU/day) helps to prevent falls and fractures in the elderly population. However, the studies are not exempt from limitations; in general, these studies were done using supplements of vitamin D combined with calcium, so the effect attributable specifically to the vitamin D is difficult to determine. In addition, in many cases the basal levels of vitamin D and/or calcium uptake is unknown (diet, exposure to the sun, supplements, etc.).

Vitamin B9: intervention trials with folic acid in pregnant women stated that the supplementation reduces the occurrence of neural tube defects (NTD) [37–39]. In USA for instance, the use of folic acid supplements was legally established by the end of 1990, which reduced significantly (20–27%) the prevalence of neural tube defects at birth [19]. Since then, the consumption of 400 µg/day of folic is recommended to women who want to conceive to prevent birth defects in the foetus [40, 41]. In relation to the other observed associations between folic acid and certain diseases (**Table 5**), the evidences obtained do not make possible to attribute potential benefits to supplementation. Besides, for all the statements about the supplementation with vitamins, there are studies that found negative evidence, including the two cases mentioned above (vitamin D and folic acid).

In relation to the other observed associations between individual vitamins and certain diseases (**Table 5**), the evidences do not clearly show direct effects of supplementation, either in a positive way (prevention of chronic diseases and/or improvement of human health) or negative (adverse effects linked to the excessive intake), due to the inadequate methodology of the existing studies [42]. There is a need for new designs of scientific studies to reach valid conclusions. These new designs should consider several aspects such as (i) the initial nutritional status of patients, (ii) the use of homogeneous groups, (iii) the use of control groups and (iv) control of the composition of the ingested food (as it often overestimates the amount of vitamin because it does not consider the bioavailability).

On the other hand, population differences based on genetics could have significant implications in terms of vitamins bio assimilation [43]. The biochemical individuality and the lack of margins for the safety of vitamins sustain the basic premise of the toxicology ‘the dose makes the poison’. To evaluate the therapeutic efficacy of a vitamin is essential to analyse the dose to be administered, the form of the vitamin used (solution, microencapsulated or crystallised), the source of the vitamin (synthetic or purified from natural sources), the bioavailability and the interaction of a specific vitamin with other nutrients.

Summarising, the analysis set out in this work shows that ‘new’ potential benefits have been attributable to several vitamins. However, most of them are not robustly supported by evidences. In addition, the analysis suggests that the information related to individual vitamins for the prevention and/or treatment of diseases is more consistent than that of a multivitamin complex. In this sense, a systematic review carried out in the USA concludes that the evidence is insufficient to support the use of multivitamin supplements to prevent chronic degenerative diseases [42].

Finally, it is not surprising that numerous studies published in more than a decade have related some supplements (including vitamins E, C, D, A, and B) with adverse effects on human health. A meta-analysis of 67 trials showed that supplements of vitamin E, vitamin A and beta-carotene might be associated with a higher incidence of mortality [44]. Another study found a higher incidence (18%) of lung cancer and mortality from all causes (8%) in men who received beta-carotene [45]. In 2008, a large randomised controlled trial was stopped after reporting that supplementation of vitamin E and selenium resulted in an increase in the incidence of prostate cancer [46].

## 6. Use of multivitamin complexes and potential risk of hypervitaminosis

The rate of use of vitamins, minerals and other bioactive compounds available in food or dietary supplements is increasing significantly in advanced societies, especially in USA population, where the multivitamin complexes are the most commonly used supplements [47–49]. Several works state that currently, more than 47% of men and 59% of the women in the USA use supplements for health benefits, and the number of users is growing significantly [50]. In Europe, the greatest consumption was observed in the countries of the north, especially in Denmark (51.0% among men, 65.8% among women) [51].

Due to this high market demand, the number of companies producing this kind of dietary supplements is increasing around the world (<http://biomarket.cat/es/69-vitaminas>; <http://salud.bayer.es/vitaminas-y-complementos-alimenticios/otras-vitaminas/>; <http://lifestylemarkets.com/vitamins-and-supplements/multivitamins/>).

There are reports indicating that there could be adverse effects on human health attributable to high consumption of multivitamin complexes. Almost 60,000 cases of toxicity by use of vitamins are reported annually USA poison control centres [<http://www.aapcc.org/annual-reports/>; [52]]. The most common adverse effects associated with excessive intake of vitamins (hypervitaminosis) are shown in **Table 3**, Section 2.3. Fat-soluble vitamins, for instance, due to its ability to accumulate in the body, have a greater potential for toxicity than water-soluble vitamins. However, the overdose of water-soluble vitamins can also cause toxicity affecting several body systems including the nervous system [20, 53]. Between the fat-soluble vitamins, the more toxic are vitamin A and vitamin D. The toxicity of vitamin A can be acute or chronic (IOM, 2006) and high doses cause many toxic manifestations (**Table 3**, Section 2.3). However, there has been no toxic effects of carotenoids (provitamin A), even when eaten in large amounts for weeks or years [41, 54], except for an orange/yellow colouring of the skin [55]. Vitamin D is potentially toxic, especially to small children [56]. In comparison to vitamins A and D, vitamin E is the least toxic when ingested orally [57]. In the case of vitamin K, toxic effects have not been observed even intaking large amounts over a long period [41]; however, a synthetic form of Vitamin K (menadione) has been associated with liver damage, and therefore no longer used therapeutically [18, 41].

The evidence on the safety profile of multivitamin complexes in humans has been established through case reports. However, the data reported from these case reports do not

allow the accurate identification of maximum tolerable intake level (U). Besides, the toxicological data show that the margins of safety for multivitamin complexes intake are not yet defined, noting toxic doses significantly different in the scientific literature. This suggests that high doses of vitamins, especially of fat-soluble vitamins, should not be given to any group of the population until the safety of such doses is well established and based on scientific evidence.

## 7. Conclusion

Despite a large number of research works carried out to study the effects of vitamins in human health during the last decades, evidences to attribute potential benefits of vitamins supplementation on either human health or prevention and/or treatment of chronic degenerative diseases are still scarce. The analysis of the research works published during the last 27 years shows that it is impossible to establish robust and universal conclusions about the benefit of vitamin supplementation on human health beyond the prevention and/or treatment of deficiency states (stated during the second half of the twentieth century).

On the other hand, it is important to highlight the high heterogeneity in the clinical and methodological experiments as well as in the tools used to perform these studies, which contributes to making difficult a comparative analysis at large scale. Clinical trials of high methodological quality and a significant number of patients are yet to come. Due to these reasons, the widespread use of multivitamin complexes as diet supplements is still not fully justified.

The most prudent recommendation and scientifically supported for disease prevention is to eat a balanced diet with an emphasis on fruits and vegetables rich in antioxidants [58], since it is through the diet it is impossible to eat excessive quantities of vitamins. This approach minimises the risk of micronutrient deficiency or excess. However, not all individuals maintain a balanced diet for long periods of time. For this reason, certain circumstances (pregnant women, infants without breastfeeding, vegetarian individuals, elderly, etc.) may require the use of vitamin supplements under control to prevent deficiencies.

Although the potential of the vitamins in the promotion of human health is enormous, it is necessary to assess the risk/benefit ratio in each case. There is much more research to be done to understand the benefits of supplementation in the prevention of diseases and the improvement of human health. Accurate studies about consumption of vitamins by country (including aspects as sex, age, etc.) as well as about food fortification and vitamins protection and stabilisation are yet to come [28]. A greater knowledge in this area of the science of nutrition will have an impact on clinical practice dietetics and nutrition guidelines for public health.

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