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Dietary supplements for human health. What do we really know? A systematic review of umbrella reviews

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Abstract

Background and objective. The potential benefits of dietary supplements for human health have been known since ancient times, but high-quality evidence on their efficacy is lacking. Furthermore, the overwhelming amount of available studies contributes to the vagueness of this topic. The aim of this systematic review was to summarize the evidence on the health benefits of dietary supplements.

Methods. A Medline search (via PubMed) was performed.

Results. 62 umbrella reviews (also known as reviews of reviews) were retrieved. Most of the results/findings (41.3%) suggested potential beneficial effects of dietary supplements on human health, but with low to very low certainty of evidence. Twenty results/findings (26.7%) supported the efficacy of dietary supplements in improving biochemical parameters and preserving human health, with moderate to high certainty of evidence. All other studies showed uncertain/conflicting results or inefficacy.

Conclusions. The demonstration of the beneficial properties of dietary supplements is far from conclusive and high-quality studies are needed.

Key words

- dietary supplements
- natural products
- efficacy
- review of reviews
- umbrella reviews

INTRODUCTION

Dietary supplements (or food supplements) are defined by the US Food and Drug Administration (FDA) as "vitamins, minerals, herbs or other botanicals, amino acids or other dietary substances to be used to supplement the diet" [1], and by the Directive 2002/46/EC of the European Parliament and the Council as "concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form (such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders) designed to be taken in measured small unit quantities" [2-4]. Although they have only been regulated for a few decades, the potential effects of minerals, vitamins, and botanicals on human health have been known since ancient times [5]. One of the earliest documents on "phytotherapy", known as the Egyptian "Ebers papyrus", dates to 2900 BC and includes more than 700 plant-based health remedies, such as onion, garlic, and pomegranate [6, 7]. In 2600 BC, an additional "list" of natural products with potential benefits for human health was represented in cuneiform on clay tablets by an unknown scholar from Mesopotamia [6]. A few centuries later, the Greeks and Romans used "medicinal herbs" to treat seasonal ailments, respiratory disorders, headaches, heartburn, and a wide plethora of "minor" conditions (e.g., wounds and burns) [6, 7]. The "cult" of natural products in the Middle Ages was preserved in the monasteries of Germany, England, France, and Ireland and was gradually enriched with Chinese, American and Indian herbs by the Arabs, Marco Polo and Vasco Da Gama [6, 7]. Until the isolation of alkaloids from pomegranate, ipecacu-

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anha, and poppy in the early 19th century, which opened the new era of "medicinal chemistry", the use of natural products remained the only remedy for the prevention and treatment of many diseases [5, 8]. However, the advent of pharmaceutical sciences did not spell the demise of phytotherapy. In fact, many drugs currently used in clinical practice are directly isolated from plants (e.g., paclitaxel and morphine) [9], and natural products are widely used as "alternative" medicines, although their efficacy is mainly based on traditional or folk use. In recent decades, the concept of "rational phytotherapy", based on the identification and study of specific active components from plants, has been introduced [7], but this has led to a confusing scenario. Indeed, there is an impressive number of preclinical and clinical studies evaluating the pharmacological value of plant-derived compounds, but they are very heterogeneous in terms of animals/population selected, choice of intervention, dosage, follow-up period and results. The lack of rigorous studies on the ability of vitamins and minerals to maintain, support, or optimize physiological functions also represents a limitation. These supplements can correct deficiencies and contribute to general homeostasis (e.g., vitamin C for scurvy, vitamin D and calcium for bone metabolism, vitamin K for bleeding disorders) [2, 10]. However, over-the-counter products are often used by individuals without signs and symptoms of deficiency, especially in Europe and North America, despite the lack of conclusive evidence regarding their role in supporting physiological balance in such population [10-12]. Thus, there is a kind of "boilerplate" that does not allow us to understand the role of dietary supplements in the "real world" context. The aim of this systematic review of umbrella reviews is to summarize what is known and highlight what is missing regarding the health benefits of dietary supplements, to shed light on this controversial and debated field.

MATERIALS AND METHODS

Study identification and selection

We launched the search string on Medline on June 1st, 2023. Therefore, data on studies published in 2023 are not complete. Our goal was to set up a search strategy to identify reviews of reviews (also known as umbrella reviews) investigating the effects of dietary supplements on human health. We combined search queries containing terms as "food", "dietary", "herbal", "nutritional", "nutraceutical", "natural" as well as "supplements", "remedies", "substances", "ingredients", "dietary supplements" (and related terms), "phytotherapy" using the Boolean operators "AND" and "OR". Filters to identify only studies conducted on humans and written in English were applied (for further detail on search strategy see *Table S1 available online as Supplementary Materials*).

We carried out duplicates detection and the whole screening process of titles and abstracts using the Rayyan tool [13]. The screening was independently carried out by three Authors (EP, MAM and EL).

After duplicates removal, we identified additional studies conducted on animals that had not yet been excluded by applying the previous filters. In particular, records containing terms that referred to studies not conducted on humans in the title such as "animal", "mice", "rat", "murine", "rodents", "rodent", "rabbit", "piglets", "canine", "broiler" were removed.

Then we selected only those records containing keywords such as "meta-analysis", "meta-analyses", "review", "reviews", "systematic review" in the title. Further screening was carried out using other keywords as "umbrella review", "overview of evidence", "overview of reviews", "overview of systematic reviews", "review of reviews", "review of evidence", "review of meta-analyses", "summary of evidence" and "summary of systematic reviews" to obtain the final set of studies assessed for eligibility.

Three Authors (EP, MAM and EL) checked the abstracts of potentially includible umbrella reviews and excluded those that did not fulfill the inclusion criteria.

Inclusion criteria

The inclusion criteria were formulated according to the Population, Intervention, Control, Outcome, and Study design (PICOS) framework.

Population (P): healthy subjects or patients with various types of disease, of any age group, including children, adults, or pregnant women. Umbrella reviews were also included when the population was unspecified, provided it was clear that only human studies were considered. Intervention (I): dietary supplements, regardless of dosage form and route of administration. Control (C): not required. Outcome (O): any effects on human health. Study design (S): umbrella reviews.

Exclusion criteria

We excluded articles that were not umbrella reviews, did not investigate dietary supplements, or did not directly evaluate health outcomes.

Data extraction from the umbrella reviews

For each umbrella review included, we extracted the following information, if reported: number of reviews included classified by type (i.e., systematic review, systematic review with meta-analysis, meta-analysis only); total number of primary studies included or descriptive statistics (mean and standard deviation or median and range) on the number of primary studies in each included review; study design of the primary studies; total number of patients included or descriptive statistics (as above) on the number of patients in each included review; characteristics of the population.

For each umbrella review, a summary of the main results was also provided and, if available, the level of certainty of the conclusions (high/moderate certainty, low certainty, inconclusive) was reported.

Data collection was carried out by two Authors (EP and MAM), using the spreadsheet software Microsoft Excel. Any discrepancies were discussed with a third Reviewer (EL).

RESULTS AND DISCUSSION

Identification and selection of umbrella reviews

Overall, 124,298 records were identified via Medline. After duplicates removal, 121,360 records were selected and screened. Among the 106,313 studies on hu-

mans, 7,105 reviews and meta-analyses were identified. Of them, 122 were finally assessed for eligibility. 62 umbrella reviews were included according to the defined exclusion criteria and 60 were excluded. The complete workflow leading to the inclusion of 62 studies is summarized in the flow chart (*Figure 1*).

The identified records were then plotted by year of publication, considering all the 121,360 non-duplicated records selected in Medline (*Figure 2a*).

Studies directly investigating or summarizing evidence on the effects of the consumption of different dietary supplements on human health have been published since 1945. The number of published papers per year shows little increase for some decades and then around the beginning of the last century an exponential growth starts, with the highest number registered to date during 2021 (9,174 studies).

All the 121,360 identified records were also grouped by the country of publication of the study, which is intended as the authors' affiliation declared country. In case of affiliations belonging to different countries in one paper, each country is counted as 1. The leading publishing country is USA, followed by China and UK (*Figure 2b*).

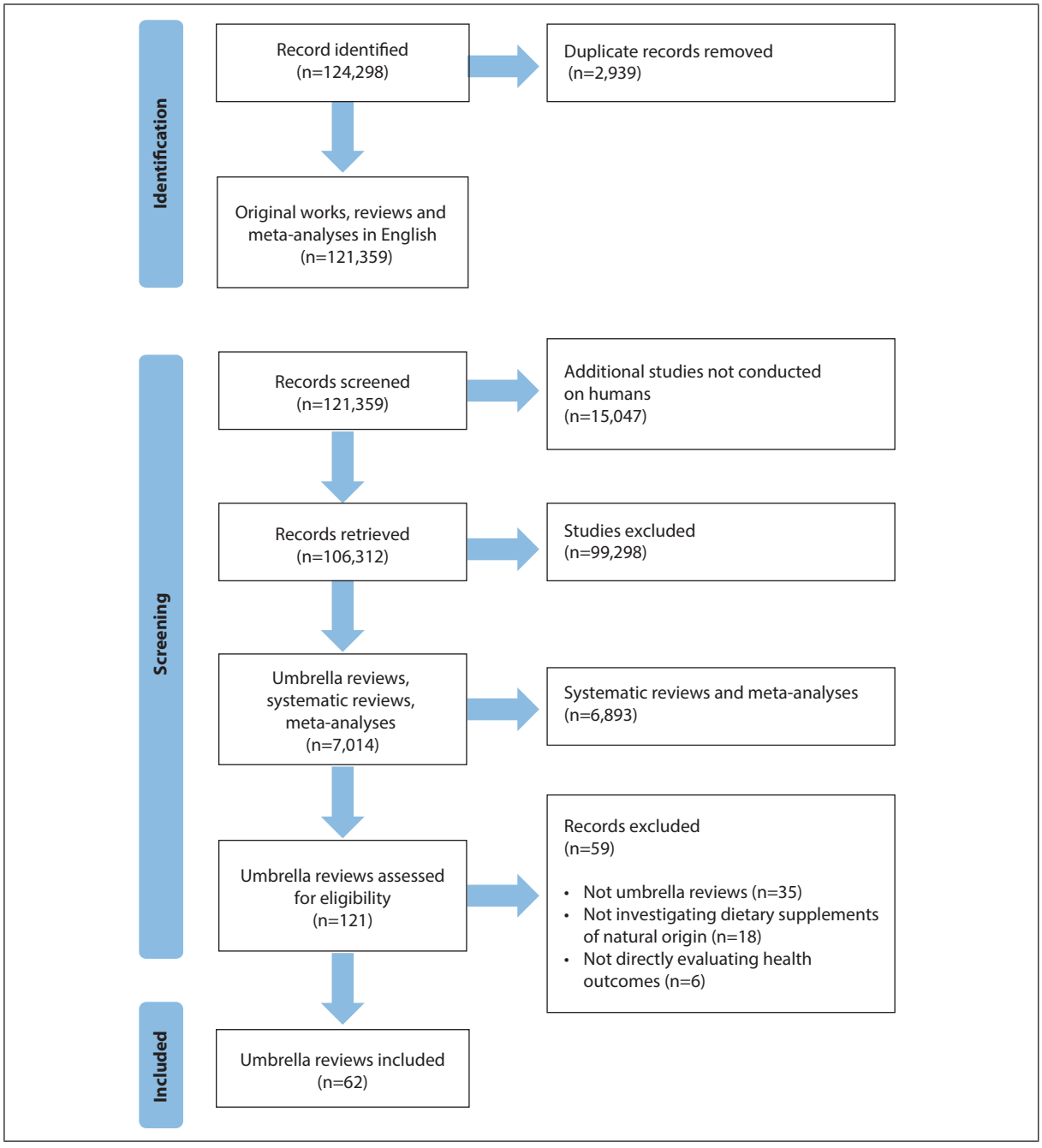

Figure 1
Flow chart of search.

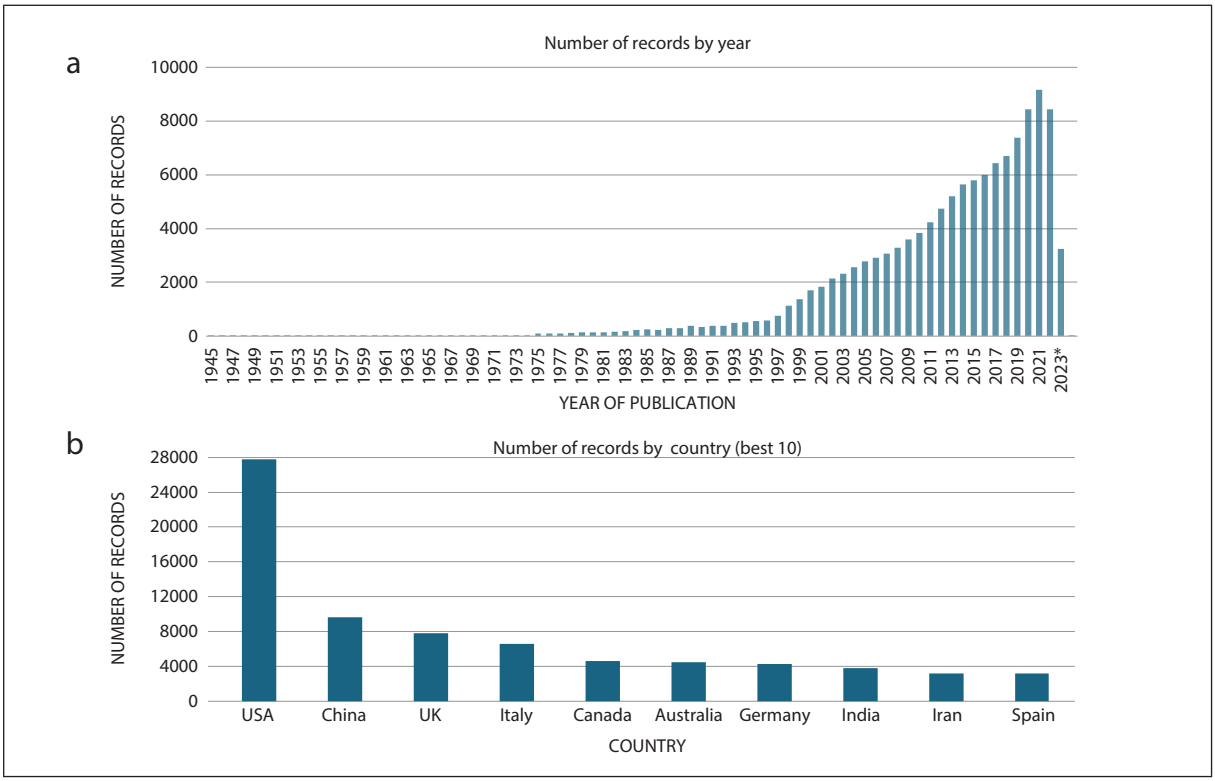

Figure 2
a) Number of non-duplicated records identified on Medline, by year of publication; b) number of non-duplicated records identified on Medline ranked by the best 10 countries of publication.

Figure 3a shows the 7,015 systematic reviews and meta-analyses (including umbrella reviews) obtained during the screening process.

Studies resuming the evidence of the effects of the consumption of different dietary supplements on human health have been published since 1976.

The trend is similar to that illustrated in *Figure 2a*. In fact, the number of published systematic reviews is steady until the beginning of the last century, then an exponential increase is observed with the highest number of published systematic reviews to date in 2021 (1,008).

The same 7,015 records were also plotted by country of publication, which is extracted from authors' affiliation country. As above, in case of authors' affiliations belonging to different countries in one paper, each country is counted as 1 (*Figure 3b*). The leading publishing country is China, followed by USA and Iran.

The number of published umbrella reviews over the years was plotted considering only the 62 records included (*Figure 4*). Umbrella reviews on the effects of the consumption of different dietary supplements have been published since 2011. In particular, an increasing publishing trend seems to be observed since 2018, with the highest number reached in 2022 (21 studies).

Systematic review

Table 1 summarizes the general characteristics of the included reviews. Twenty-four (35.8%) were reviews of systematic reviews (SRs) [14-37], 19 (28.4%) were reviews of meta-analysis (MA) [38-57], 21 (31.3%) were reviews of SRs with MA [14, 15, 19, 58-75], and 3 (4.5%) were i) reviews of Mendelian randomisation studies and SRs [23], ii) reviews of MA and umbrella reviews [39], or iii) reviews of Mendelian randomisation studies and MA [45] (some umbrella reviews included more than one type of review). The number of studies on dietary supplements included in each review ranged from one to 289, and the interventions were very heterogeneous. In fact, forty-six reviews focused on the effects of vitamins [16, 17, 21, 23-25, 28, 29, 32-34, 39, 41, 44-46, 49, 55, 57, 59-61, 65, 68, 71, 73], 21 of minerals [24, 28, 32, 34, 36, 39, 41, 47, 60, 67, 72], 11 of omega-3 fatty acids [17, 21, 24, 39, 42, 44, 46, 47, 52, 56, 62], 10 of prebiotics/postbiotics/synbiotics [17, 18, 26, 27, 38, 39, 46, 48, 53, 74], 10 of proteins and amino acids [15, 17, 19, 29, 35, 69], one of lipid-based nutrients [44], 28 of others interventions/supplements (e.g., curcumin [30, 46, 51, 64], *Camellia sinensis* L. – green tea [31, 64, 66, 67], coenzyme Q10 [20, 24], unspecified antioxidants [21, 63], polyphenols [39, 54], *Allium sativum* L. (garlic) [31, 50]). Some reviews have focused on more than one dietary supplement.

Details on the characteristics of each study are given in *Table S2 available online as Supplementary Materials*. Overall, the population was highly heterogeneous, ranging from healthy to chronically ill people, with a high risk of overlap between patients and/or studies. Twenty results/findings (26.7%) supported the efficacy of dietary supplements in improving biochemical parameters (such as inflammatory biomarkers and fasting

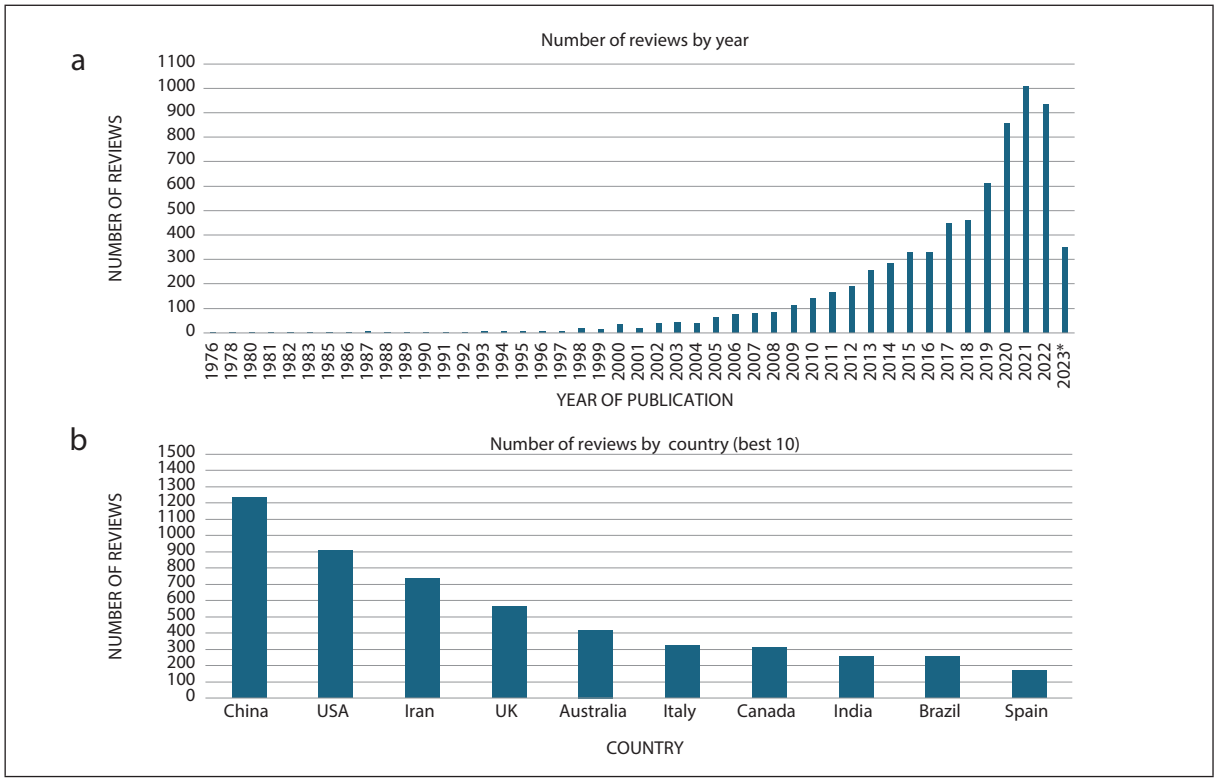

Figure 3
a) Number of non-duplicated systematic reviews and meta-analyses identified on Medline, by year of publication; b) number of non-duplicated systematic reviews and meta-analyses identified on Medline ranked by the best 10 countries of publication.

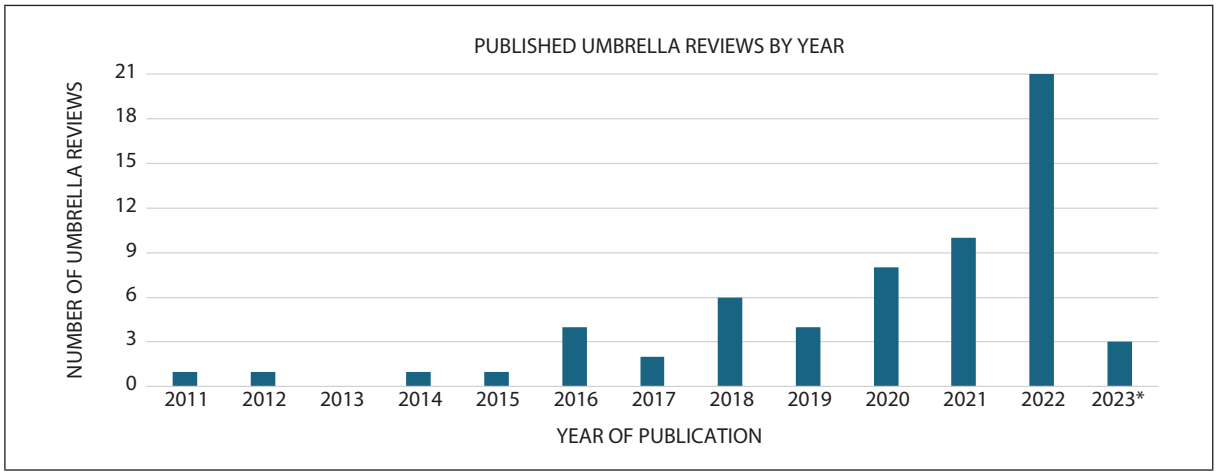

Figure 4
Number of published umbrella reviews investigating the effects of dietary supplements on human health outcomes by year of publication.

glucose) and in preserving human health (e.g., by reducing the risk of anemia, migraine and fractures), with moderate to high certainty of evidence. Most studies focused on vitamin D supplementation and demonstrated its efficacy in reducing the risk of falling in adult patients when administered in the elderly at risk of malnutrition and in the elderly with dementia (risk reduction ranging from 14.0% to 19.0%) [68]. Furthermore, vitamin D supplementation (8-24 weeks) has been associated with a slight, but not significant, reduction in insulin resistance (standardized mean difference, SMD, compared with placebo [95% confidence interval, CI]: -0.25 [-0.53, 0.04] for the homeostatic model assessment index – HOMA index) [46]. In this regard, other dietary supplements could improve glucose, lipid and adipose tissue metabolism. For example, curcumin supplementation (6-12 weeks) reduced fasting glucose levels in women with polycystic ovarian syndrome (SMD

Table 1
Summary of the included studies

Type of the umbrella reviews, n (%)*; median number of the included studies [range]	
Reviews of SRs	24 (35.8%); 15 [5-87]
Reviews of MA	19 (28.4%); 30 [1-195]
Reviews of SRs with MA	21 (31.3%); 12 [4-141]
Others**	3 (4.5%); 74 [13-289]
Main findings, n (%)* **	
Efficacy with low certainty/insufficient evidence or without information on the quality of evidence	31 (41.3%)
Efficacy	20 (26.7%)
Inefficacy with low certainty/insufficient evidence or without information on the quality of evidence	13 (17.3%)
Inconclusive/conflicting results	8 (10.7%)
Inefficacy	3 (4.0%)
Intervention/supplements, n (%)	
Vitamins	46 (74.2%)
Vitamin D	20
Vitamin C	6
Vitamin D + calcium	4
Vitamin B9 (folic acid)	3
Vitamin A	3
β-carotene (precursor of vitamin A)	2
Vitamin E	2
Vitamin B complex	1
Vitamin B3 (niacin)	1
Vitamin B6	1
Vitamin B7 (inositol)	1
Vitamin B12	1
Vitamin K	1
Minerals	21 (33.9%)
Zinc	3
Iron	3
Iron + vitamin B9 (folic acid)	3
Calcium	4
Selenium	3
Chromium	2
Magnesium	1
Iodine	1
Zinc + iron	1
Omega-3 fatty acids	11 (17.7%)
Prebiotics/probiotics/synbiotics	10 (16.1%)
Proteins and amino acids	10 (16.1%)
β-hydroxy-β-methyl butyrate (leucine metabolite)	2
Glutamine	1
Tryptophan	1
Leucine	1
Not specified	5
Lipid-based nutrients	1 (1.6%)
Others	28 (45.2%)
Curcumin	4
Camellia sinensis L. (green tea)	4
Coenzyme Q10	2
Antioxidants (unspecified)	2
Polyphenols	2
Allium sativum L. (garlic)	2
Phytosterols, *Serenoa repens*, β-sitosterol, *Pygeum africannum* Hook f. and Cernilton (rye grass pollen)®	2
Pollen	1
Spicy foods and chili pepper	1
Caffeine	1
Zingiber officinale Roscoe (ginger), *Hibiscus sabdariffa* L., *Aloe vera* spp., *Nigella sativa* L., or *Arthrospira platensis* (spirulina)	1
Cannabis sativa spp. and *Rosa canina* L.	1
Cinnamomum verum Presl (cinnamon)	1
Fish oil	1
Vegetable oil	1
Guar gum, chromium picolinate, *Ephedra* spp. and ephedrine, *Citrus aurantium* L., conjugated linoleic acid, calcium, glucomannan, chitosan, *Camellia sinensis* L. (green tea)	1
Sodium bircarbonate	1

MA: meta-analysis; SRs: systematic reviews; *some umbrella reviews included more than one type of review; **reviews of MA and umbrella reviews (n=1), Mendelian randomisation studies and SRs (n=1), Mendelian randomisation studies and MA (n=1); ***some studies on more than one dietary supplement have reported more than one result.

compared with placebo: -3.31 [-4.89, -1.79]) [46], as well as blood lipid levels in the general population (total cholesterol, TC: -25.13 mg/dl [40.6, -9.28]; low-density lipoprotein cholesterol, LDL-C: -39.83 [75.02, 4.25] after 8-12 weeks, compared with placebo) [64]. Vegetable oils, phytosterols, plant proteins and *Camellia sinensis* L. exhibited lipid-lowering levels (vegetable oils, 2-104 weeks: -6.7 to -19.0 mg/dl for TC and -0.4 to -16.2 mg/dl for LDL-C; phytosterols, 3-85 weeks: -7.7 to -16.4 mg/dl for TC and -10.4 to -23.7 mg/dl for LDL-C; plant proteins, 3-208 weeks: -6.4 to -23.2 mg/dl for TC and -4.76 to -21.7 mg/dl for LDL-C; *Camellia sinensis* L., 2-96 weeks: -0.4 to -27.6 mg/dl for TC and -0.2 to -24.8 mg/dl for LDL-C) [64], while probiotics (8-12 weeks) decreased fasting blood glucose in adult patients (SMD compared with placebo: -4.70 [-8.43, -0.97]) [46]. Also, probiotics reduced body mass index (BMI) and waist circumference in obese people, particularly after 8 weeks of supplementation (SMD for BMI from baseline: -0.11 [-0.40, 0.18] for periods <8 weeks *vs* -0.21 [-0.32, -0.09] for 8-12 weeks; SMD for body weight from baseline: -0.25 [-0.80, 0.30] for periods ≤8 weeks *vs* -0.41 [-0.61, -0.20] for more than 8 weeks) [48].

Many reviews have focused on the effects of dietary supplements in pregnant women showing, for example, a positive association between vitamin D use and reduced risk of preterm delivery (risk ratio, RR: 0.36 [0.14, 0.93]) or low birth weight (RR: 0.40 [0.24, 0.67]) [25]. High magnesium intake [72] and omega-3 supplementation [62] decreased the intensity/frequency of migraine in pregnant women and the risk of pre-eclampsia (RR: 0.75 [0.57, 0.98]) and low-birth weight (RR: 0.72 [0.55, 0.94]), respectively. Finally, vitamin A increased retinol concentrations in maternal serum and breast milk and reduced the risk of anemia and maternal clinical infection in women of reproductive age [32].

Consistent results have been found regarding the anti-inflammatory effects of dietary supplements. For instance, C-reactive protein (CRP) levels were significantly reduced by vitamin C, zinc and melatonin supplementation, while tumor necrosis factor (TNF) and interleukin (IL)-6 levels were significantly lowered by melatonin supplementation. The effects of vitamin D on inflammatory markers, however, were controversial [60, 65]. Omega-3 supplementation has also shown significant effects on CRP, TNF and IL-6 levels [42]. However, beneficial effects on inflammatory biomarkers do not necessarily imply clinical efficacy in the prevention and treatment of inflammatory diseases. For instance, the double-blind, randomized, placebo-controlled ASCEND-Eye trial showed no significant benefit for omega-3 fatty acids on diabetic retinopathy [76]. Furthermore, Cochrane reviews have shown that omega-3 intake has little or no effect in preventing cardiovascular events [77], as well as dry eye symptoms in patients with dry eye disease [78].

Thirty-one results/findings (41.3%) suggested potential beneficial effects of dietary supplements on human health, but with a low to very low certainty of evidence. Although these reviews yielded promising results on the health effects of dietary supplements, some doubts remain on the methodological quality of the included studies. Finally, eight results/findings (10.7%) were uncertain/conflicting, thirteen (17.3%) suggested that dietary supplements are ineffective (certainty of evidence low to very low), and only three (4.0%) concluded that dietary supplements have no beneficial effects on human health (certainty of evidence moderate to high). In this regard, vitamin D supplementation (without calcium) did not prevent preterm birth, stillbirth and cesarean section in pregnant women [16], nor hip fracture or any other fractures in healthy individuals [25]. Furthermore, calcium supplementation had no effect on body weight and BMI in women of reproductive age [32].

CONCLUSIONS

The demonstration of the beneficial properties of dietary supplements is far from conclusive and further high-quality studies are needed to confirm the potential benefits of vitamins, minerals and botanicals in the prevention of diseases or their recurrence, with affordable costs justifying their use. In fact, in most papers the quality of the evidence was low or uncertain or even inconclusive, and the studies showed an effect mainly on biomarkers or soft endpoints. In our opinion, a more regulated process (e.g., through randomized controlled trials), simpler but somehow similar to that of drugs or substance based medical devices, is needed for dietary supplements to clearly demonstrate their benefits and justify the additional costs to patients and the community.

LIMITATIONS

This is a review of umbrella reviews, which increases the risk of missing relevant data not extracted in the original umbrella reviews or in the primary studies they included. Additionally, the selected reviews differ substantially in terms of the type and number of included studies, resulting in the variability of sample size and types of interventions considered. There is also a high risk of overlap between patient populations, potentially leading to an overestimation of the effect. In fact, several umbrella reviews on the same topic may have included the same primary studies and, consequently, the same patient data. This may have artificially increased the statistical power of the result without additional evidence or new data.

Authors' contributions

Conceptualization: AM, EL; methodology: EP, MAM, EL; software: EP, MAM, EL; investigation: EP, MAM, EL; data curation: EP, MAM, EL; writing – original draft preparation: EP, MAM; writing – review and editing: EP, MAM, VC, SDM, CG, AM, EL; supervision: AM, EL.

Conflict of interest statement

The Authors declare no conflict of interest.

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